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

Investigational Product Number:	PF-00914730
Investigational Product Name:	Dexmedetomidine hydrochloride
United States (US) Investigational New Drug (IND) Number:	32,934
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	C0801039
Phase:	3 / 4

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	27 August 2019	Not applicable (N/A)
Amendment 1	21 April 2020	General grammatical and formatting revisions & typographical error corrections Protocol Summary section: updated as appropriate to be consistent with the revisions described below Schedule of Activities (SOA) section: updated as appropriate to be consistent with the revisions described below. Section 1. Introduction: revised to provide clarification around propofol approval in the US vs Japan. Section 1.2.1. Study DEX 10-16: revised to remove trailing zeroes related to DEX dosing. Section 1.2.2.2. Dose Selection: revised to: clarify that age cohorts are based on age on Day 1; remove trailing zeroes related to DEX dosing. Section 1.3.1.1. Safety Data from Pediatric ICU Sedation Studies: revised to remove trailing zeroes related to DEX dosing. Section 2. Study Objectives

		and Endpoints: revised to: remove safety endpoint for clinically significant hemodynamic changes from Baseline; add safety endpoint for time outside of the stable range for hemodynamic parameters; clarify that incidences of listed adverse events are for protocol-specified events; add paradoxical agitation reaction as a safety endpoint. Section 3. Study Design: revised to provide allowance for Screening and Day 1 Visits to occur on different days. Section 3.2. Approximate Number of Subjects: revised to: remove the number of sites; clarify that age cohorts are based on age on Day 1. Section 4.1. Inclusion Criteria at Screening: revised to: provide separate Screening and Day 1 Inclusion Criteria; clarify that age is based on age on Day 1; require that ASA assessment is performed by medically qualified personnel and reviewed by PI; permit conditional use of a pre-existing IV for study drug administration. Section 4.2. Inclusion Criteria on Day 1: revised to add this section to confirm subject continued to meet Screening inclusion criteria.

		Section 4.3. Exclusion Criteria at Screening, revised to: separate the exclusion criteria into separate Screening and Day 1 Exclusion Criteria; modify weight criterion for global details to be done at Screening; clarify non-interventional/observational procedures are permitted during MRI; change "allergy" to "hypersensitivity" to DEX, PRO or components; remove the acute MI exclusion; add medication as a factor that may increase subject risk. Section 4.4. Exclusion Criteria on Day 1: revised to add this section and move selected Screening exclusion criteria here. Section 5.1. Allocation to Treatment: revised to add DEX total loading dose in mLs to the unblinded IRT confirmation report. Section 5.4.2. Preparation and Dispensing: revised to clarify the study drug preparation and dispensation responsibilities of the unblinded site pharmacist. Section 5.5. Investigational Product Administration: revised to: remove the requirement for a new IV to be placed; clarify age cohorts are based on age on Day 1; remove trailing zeroes from

		the dosing tables. Section 5.6. Rescue Propofol Medication: revised to: clarify the propofol maintenance dosing requirements; provide clarification around propofol approval in the US vs Japan. Section 5.10.2. Permitted Concomitant Treatments: revised to clarify gas induction procedure requirements. Section 5.10.3. Prohibited Concomitant Treatments: revised to: clarify other alpha-2 agonist/antagonist use; clarify interventional/non-interventional/observational procedures during scan and post-scan recovery. Section 6.1. Screening: revised to: provide separate Screening Visit requirements; allow 12-lead ECG to be performed in lieu of rhythm strip; remove pregnancy test from Screening. Section 6.2. Day 1 Period 1 (MRI scan): revised to: separate Day 1 assessments into pre- and post-randomization timeframes; add caveat regarding weight and temperature if Screening/Day 1 are the same day; allow for urine or whole-blood pregnancy test; clarify Baseline values are

		those obtained within approximately 5 minutes before the DEX loading dose; remove requirement for placement of a new IV. Section 6.3. Day 1 Period 2 (Post-MRI Recovery): revised to: clarify Baseline values are those obtained within approximately 5 minutes before the DEX loading dose; remove the PSSS assessments from this period; modify the PAED collection timepoint requirements. Section 6.5. Subject Withdrawal/Early Termination: revised to add a discontinuation requirement for subjects who have a medical procedure performed during the MRI scan. Section 6.5.1. Adverse Events Requiring Subject Withdrawal from Treatment: revised to add discontinuation requirement for subjects who have a medical procedure performed during the MRI scan. Section 7. Assessments: revised to: add "as appropriate" to assent collection; remove requirement for placement of a new IV; allow for urine or whole-blood pregnancy test; clarify the 12-lead ECG and blood pressure at Screening

		requirements. Section 7.1. Pregnancy Testing: revised to clarify that urine or whole blood pregnancy test will be done on Day 1. Section 8.4.1.1. Changes in Blood Pressure and Heart Rate: revised to clarify Baseline values are those obtained within approximately 5 minutes before the DEX loading dose. Section 8.5. Medical Device Complaint Reporting Requirements: revised to limit medical device reporting to sites in Japan using propofol pre-filled syringes. Section 9.1. Sample Size Determination: revised to remove trailing zeroes related to DEX dosing. Section 9.2.5. Japanese Population Set: revised to add a new analysis population set for Japanese subjects. Section 9.5. Safety Analysis: revised to: clarify Baseline values are those obtained within approximately 5 minutes before the DEX loading dose; add paradoxical agitation reaction and clarify text regarding protocol-specified adverse events summarized for each

		age cohort and each dose level; remove text regarding separate tabulations of specific AEs. Appendix 1. Abbreviations: revised to update per protocol text revisions. Appendix 4. Modified Aldrete Score: revised to add reference. Appendix 5. Pediatric Anesthesia Emergence Delirium Scale (PAED): revised to add reference. Appendix 6. Pediatric Sedation State Scale (PSSS): revised to add reference. Appendix 9. Propofol Pre-filled Syringe Medical Device Reporting in Japan; revised to add appendix.
Amendment 2	11 March 2021	Protocol Summary section: updated as appropriate to be consistent with the revisions described below. Schedule of Activities: updated as appropriate to be consistent with the revisions described below. Section 1. Introduction: revised to remove text identifying the US and Japan as participating countries; clarify PRO is not approved for procedural sedation in the pediatric population and is

		investigational in this study. Section 1.4 Safety Summary: updated the SRSD language and clarified that the propofol USPI may be referenced for additional safety information and countries may also reference their local package insert for country-specific information. Section 2 Study Objectives and Endpoints: revised the primary efficacy endpoint to clarify the comparison is in the combined age cohorts; corrected the safety endpoint to include subjects who require intervention to complete the MRI; changed the protocol-specified AE term "systolic hypotension" to "hypotension". Section 3.2 Approximate Number of Subjects: revised to remove text identifying participating countries. Section 4.3 Exclusion Criteria at Screening: modified exclusion criterion #2 to clarify that medications or vaccines approved for emergency authorization are not considered investigational and are not included in the 30-day restriction; revised exclusion criterion #22 to include ECG findings diagnostic of AV conduction block or sustained cardiac arrhythmia; eliminated "acute febrile illness" from exclusion

		criterion #26 to limit the exclusion to fever. Section 5.6 Rescue Propofol Medications: clarified requirements for propofol bolus dosing and maintenance dose increases and decreases; clarify PRO is not approved for procedural sedation in the pediatric population and is investigational in this study. Section 5.10 Concomitant Treatments: revised to extend collection of concomitant treatments through the Day 29 Long-term Follow-up Visit. Section 5.10.1 Required Treatments: revised the maintenance IV fluid requirements to require a minimum mL/hr rate per formula but also permitting a maximum rate of 100 mL/hr. Section 6.2 Day 1 Period 1 (MRI scan): added clarification that serum qualitative or quantitative hCG pregnancy tests are not permitted; clarified vital signs collection and timepoint capture. Section 6.3 Day 1 Period 2 (Post-MRI Recovery): clarified vital signs collection and timepoint capture. Section 6.4.2 Day 29 Long-term Follow-up Visit: added collection of concomitant

		treatments. Section 6.5.1 Adverse Events Requiring Subject Withdrawal from Treatment: changed the AE term "systolic hypotension" to "hypotension". Section 7 Assessments: revised to extend collection of concomitant treatments through the Day 29 Long-term Follow-up Visit; added clarification that serum qualitative or quantitative hCG pregnancy tests are not permitted; clarified requirement for 12-lead ECG vs rhythm strip including changes suggestive of AV conduction block or sustained cardiac arrhythmia; added instruction on rounding height/weight values to 1 decimal place; clarified BP cuff size must be appropriate for arm or leg girth. Section 7.1 Pregnancy Testing: added clarification that serum qualitative or quantitative hCG pregnancy tests are not permitted. Section 8.1 Requirements: updated the requirements for recording safety events on the CRF to be consistent with the current Pfizer protocol template. Section 8.1.4 Time Period for Collecting AE/SAE Information: added

		concomitant treatment data to be collected at the Day 29 Long-term Follow-up visit. Section 8.4.1.1 Changes in Blood Pressure and Heart Rate: clarified text to specify AE criteria refer to measurements exceeding the specified limits within the indicated time periods; clarified bradycardia AE definition based on 2 consecutive measurements at least 1 minute apart to ensure a minimum duration of decreased HR; changed the AE term "systolic hypotension" to "hypotension"; clarified hypotension AE definition based on 2 consecutive measurements at least 5 minutes apart to ensure a minimum duration of decreased SBP and/or requires intervention; clarified hypertension AE definition based on measurements at least 5 minutes apart. Section 8.4.1.3 Changes in Respiratory Rate, $EtCO_2$ and SpO_2: clarified bradypnea AE definition based on measurements at least 1 minutes apart. Section 8.4.5.1: Medication Errors: modified the sponsor notification timeframe requirement to 24 hours. Section 9.3.3 Analysis of Other Secondary Endpoints:

		added text when censored time would be used to calculate emergence time. CCI [redacted] Section 9.5 Safety Analysis: corrected the safety endpoint to include subjects who require intervention to complete the MRI; changed the AE term "systolic hypotension" to "hypotension". Appendix 5: Pediatric Anesthesia Emergence Delirium Scale (PAED): additional reference added. General grammatical and formatting revisions & typographical error corrections.

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PROTOCOL SUMMARY

Background & Rationale

Dexmedetomidine (DEX) is a highly selective α2-adrenergic agonist that is being investigated for use in procedural sedation in pediatric subjects undergoing magnetic resonance imaging (MRI) requiring moderate to deep sedation. DEX is currently approved for sedation of initially intubated and mechanically ventilated adults during treatment in an intensive care setting and for procedural sedation of adults.

The present study is being conducted by Pfizer, Inc under the Pediatric Research Equity Act (PREA) and is a Phase 3/4 randomized, double-blind, dose-ranging study of the safety and efficacy of DEX used with propofol (PRO) for procedural sedation of pediatric subjects ≥1 month to <17 years of age undergoing MRI scans.

Objectives

- The primary efficacy objective is to 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 the combined age cohorts who do not require concomitant PRO to achieve adequate sedation.

- The key secondary objective is to 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 do not require concomitant PRO to achieve adequate sedation.

- Other secondary efficacy objectives include:

  - 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 do 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.

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- The safety objective is to assess the safety of DEX used for procedural sedation of pediatric subjects undergoing an MRI scan.

Endpoints

- Primary Efficacy: Percent of subjects at the DEX high dose level versus the low dose level in the combined age cohorts who do not require concomitant PRO to complete the MRI.

- Key Secondary Efficacy: Percent of subjects at the DEX high dose level versus the low dose level in each age cohort who do not require concomitant PRO to complete the MRI.

- Secondary Efficacy:

  - 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 do 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 dose level who receive 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.

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- Safety:

  - Incidence, seriousness, causality and severity of treatment-emergent adverse events.

- 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 of bradypnea, hypoxia and apnea.
- Incidence of protocol-specified cardiac adverse events of hypotension, hypertension and bradycardia.
- Incidence of protocol-specified adverse event of paradoxical agitation reaction.
- Incidence of protocol-specified adverse events of bradypnea, hypoxia, apnea, hypotension, hypertension, bradycardia and paradoxical agitation reaction requiring intervention.
- Incidence of DEX withdrawal-related adverse events after discontinuation of DEX infusion.

Study Design

This is 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 subjects ≥1 month to <17 years of age undergoing MRI scans. The sponsor, subject and investigator will be blinded to the dose of DEX.

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

A sufficient number of subjects will be screened to randomize approximately 120 subjects (40 subjects 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 subjects will receive double-blind treatment where one of 3 dose levels of DEX will be administered. Following completion of required procedures before randomization at the Day 1 Visit, subjects meeting entry criteria will be randomly assigned to a Low, Middle or High dose level group (actual dose dependent on age) in a 1:1:1 ratio.

Treatment will be initiated just prior to the start of the MRI scan and will continue during Period 1 (MRI scan). Subjects will first receive a DEX loading dose administered over 10 minutes. Following completion of the loading dose, the maintenance infusion of DEX will be started. The subject's level of sedation will be assessed using the PSSS at 5-minute intervals throughout the drug infusion. If an adequate level of sedation is not achieved as assessed by the investigator (eg, if the subject moves) within 5 minutes after the DEX maintenance infusion has been started, concomitant PRO may be given to ensure that an adequate sedation level is achieved and maintained for completion of the scan. Sedation with DEX and if required, concomitant PRO, shall continue through completion of the MRI scan, to maintain the subject at an adequate sedation level per principal investigator (PI) clinical judgment. The target sedation level is indicated by a PSSS score of 2. Subjects will also be administered supplemental intravenous (IV) fluids throughout the DEX infusion at a maintenance rate per Section 5.10.1 Required Treatments. The use, type and rate of maintenance fluid administration following discontinuation of the DEX infusion will be at site discretion.

The investigational product infusion(s) should not be discontinued until confirmation that the MRI is complete has been received and DEX must be discontinued prior to the subject being transferred to the post-procedural recovery area. Period 2 (post-MRI recovery) begins at the conclusion of the MRI scan.

Investigational Product Administration

The study will be conducted using the manufactured strength of DEX 200 mcg/2 mL, diluted to a concentration directed by the Investigational Product Manual (IP Manual) based on each subject's treatment group assignment.

Subjects enrolled into the study will be randomized to receive one of three DEX dosing regimens (Low, Middle, or High), each consisting of an IV loading dose that is immediately followed by an IV maintenance infusion that will continue for the duration of the MRI scan.

The loading and maintenance infusion doses will be given at the stable, pre-defined doses as described below and may not be modified, but the infusion may be discontinued if clinically indicated. The loading dose will be administered over 10 minutes:

Blinded dose levels for subjects ≥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

Blinded dose levels for subjects ≥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

Rescue Propofol Administration

Once the DEX loading dose has been administered and the maintenance dose started, if an adequate level of sedation is not achieved within 5 minutes after the start of the DEX maintenance infusion, concomitant PRO may be given per clinical judgment to ensure that an adequate level of sedation is achieved to start the scan. The target sedation level is indicated by a PSSS score of 2.

Concomitant PRO should be administered as needed through completion of the scan to maintain adequate subject sedation per PI clinical judgment. If it is needed, concomitant PRO should 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 be given as needed for subject movement/wakening. Following each additional PRO bolus, there must be 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 be made in 25 or 50 mcg/kg/min increments without a corresponding PRO bolus. The PRO maintenance infusion may also be decreased in 25 or 50 mcg/kg/min increments as needed to maintain adequate subject sedation, or it may be discontinued if clinically indicated.

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

Statistical Methods:

Sample Size

The primary comparison will be the percent of subjects who do not require supplemental PRO in the high dose group vs. the low dose group in both age cohorts combined. The younger age cohort will be comprised of subjects aged ≥1 month to <2 years of age and the older age cohort will include subjects ≥2 to <17 years of age. The primary efficacy analysis population is the Full Analysis Set (FAS) defined as all randomized subjects who receive any amount of DEX, and for the primary and key secondary analyses, subjects who do not complete the MRI scan will be considered failures, ie, will be counted as receiving supplemental PRO. Assuming that the percent of subjects not requiring PRO are 15% and 60% in the low and high dose groups respectively, a sample size of 40 per dose group would provide a 99% power for a 2-sided test with alpha=0.05. The key secondary comparison is the percent of subjects who do not require supplemental PRO in each of the 2 age cohorts. Assuming that the percentage of subjects not requiring supplemental PRO in the older age cohort is 17% and 63% for the low and high dose groups respectively, and the percent of

subjects not requiring PRO in the younger age cohort is 13% and 57% for the low and high dose groups respectively, and assuming that equal number of subjects will be enrolled in each age cohort, the power = 87% for the older age cohort and 86% for the younger age cohort. Within the older age cohort, it is planned to enroll approximately 4 subjects per dose group for subjects ≥12 to <17 years of age, since it is expected that these subjects would require minimum sedation. Forty subjects will be enrolled per each dose level, and 20 subjects for each dose group for age cohorts ≥1 month to <2 years and ≥2 years to <17 years.

Analysis Populations:

Safety Analysis Set

The safety analysis set consists of all randomized subjects who received any amount of DEX. Participants will be analyzed according to the intervention they received. In the event a subject receives a loading and/or maintenance dose that is different from the dose group to which they were randomized, the subject will be analyzed in the dose level group that corresponds to the lowest dose received. All safety analyses will be performed on the safety analysis set.

Full Analysis Set (FAS)

All randomized subjects who receive any amount of DEX will form the FAS. Participants will be analyzed according to the intervention to which they were randomized. This will be the primary population for efficacy analysis.

Efficacy Evaluable Population (EEP)

All randomized subjects who receive any amount of DEX and complete the MRI scan will form the EEP.

Per Protocol Population (PPP)

All subjects included in the FAS and have no major protocol deviations will form the PPP. The details of the major protocol violation criteria will be documented in a separate document prior to the end of the study.

Japanese Population Set (JPS)

All randomized Japanese subjects who receive any amount of DEX will form the JPS. The JPS will be used for efficacy endpoints, demographic and baseline characteristic and safety endpoints. Participants will be analyzed according to the intervention to which they are randomized for efficacy and will be analyzed according to the intervention they receive for safety.

Endpoint Analyses:

Primary Efficacy Endpoint Analysis

The DEX high vs low dose group will be compared by Mantel-Haenszel test, and by calculating the odds ratio and 95% confidence intervals on the percent of subjects not requiring supplemental PRO. All age cohorts will be combined. The primary analysis will be performed based on the FAS. The same analysis will be repeated on the EEP and PPP.

Analysis of Key Secondary Efficacy Endpoint

The method of analysis for the primary endpoint will be repeated for the key secondary endpoint for each age cohort based on the FAS. The same analysis will be repeated on the EEP and PPP.

Analyses of Other Secondary Efficacy Endpoints

The method of analysis for the primary endpoint will be repeated for the secondary endpoints comparing the low dose to the medium dose and the medium dose to the high dose, overall and within each age cohort based on the FAS, EEP and PPP.

The total amount and the weight and time adjusted amount (per kg per minute) of PRO use will be summarized for each dose group with descriptive statistics (N, mean, standard deviation [SD], median, minimum, Q1, Q3, and maximum). The weight- and time-adjusted difference between treatment groups (high dose and low dose, and medium dose and low dose and high dose versus medium dose) will be assessed using two-way analysis of variance (ANOVA) when assumption of normal distribution is reasonable or by nonparametric tests when this assumption is not met.

Emergence time (defined as the time from the end of the MRI scan to when the subject meets a Modified Aldrete Score ≥9) will be summarized and compared between dose groups using Kaplan Meier methodology. Subjects who are withdrawn or discharged from the recovery area without reaching an Aldrete score ≥9, will be considered as having censored time computed from the end of the MRI scan to the time of the last vital signs assessment. Zero minute will be used as the censored time if no vital signs are taken during the post-MRI recovery period.

Additionally, the difference between dose levels in percent of time at the target sedation rating scale score (PSSS rating of 2) following the administration of the DEX loading dose and during the DEX maintenance infusion will be assessed using the Wilcoxon test.

Time (minutes) from the onset of the DEX infusion to the first dose of PRO will be summarized using the Kaplan-Meier method. Subjects that do not receive any additional PRO will be considered as having a censored time. The censored time to the first dose of PRO for additional sedation will be computed as the length of time from the onset of the DEX infusion up to the time the DEX infusion is stopped.

Efficacy analyses will be conducted for all age cohorts combined and by each age cohort.

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Analysis of Safety Endpoints

All safety analyses will be performed on the safety analysis set.

Descriptive statistics (quantitative variables: arithmetic mean, SD, median, minimum, and maximum, categorical and ordinal variables: proportion of subjects) will be calculated for quantitative safety data as well as for the change from baseline, when appropriate. Data analyses will be presented by dose level, overall and within each age cohort.

TEAEs will be analyzed by dose level, overall, and for each age cohort according to the Medical Dictionary for Regulatory Activities system organ class and preferred term. Additionally, the proportion of subjects with protocol-specified adverse events of bradypnea, hypoxia, apnea, hypotension, hypertension, bradycardia and paradoxical agitation reaction and the proportion of subjects with such events requiring intervention will be summarized for each age cohort and each dose level. Pre-specified criteria will be used to identify the protocol-defined adverse events mentioned above.

The proportion of subjects who completed the MRI scan and required artificial ventilation or intervention to restore baseline or normal hemodynamic status will also be summarized. The incidence of individual adverse events during MRI sedation will be descriptively summarized for each dose level, including the total adverse events.

The types of individual interventions and the total number of interventions will be descriptively summarized at each dose level and for each age cohort (ie, airway repositioning, bag-mask intervention, deepening of sedation, fluid bolus, jaw thrust, continuous positive airway pressure (CPAP), increased oxygen, intubation, etc).

Vital sign measurements and hemodynamic and respiratory parameters will be summarized descriptively by dose level and age cohort.

Prior and concomitant medications will be summarized according to WHODRUG Dictionary. The number and percentage of subjects who used prior medications (by preferred term) will be tabulated by dose level and age cohort. The number and percentage of subjects who used concomitant medications will be similarly tabulated.

DEX withdrawal symptoms, such as agitation/anxiety, rebound tachycardia and rebound hypertension will be summarized by each dose level and age cohort. A descriptive summary will be performed for the incidence of DEX withdrawal-related AEs after discontinuation of the DEX infusion.

Descriptive analyses will be performed for the Pediatric Anesthesia Emergence Delirium Scale (PAED) total score for dose level and by age cohort.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol. The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities table, to in order to conduct evaluations or assessments required to protect the well-being of the subject.

Study Visit Identifier	**Screen**	**Day 1 (Day of MRI scan)**		**Day 2 Follow-up**	**Day 29 Long-term Follow-up**
Study Visit Scheduling/Window	**Screening (up to 3 days before-randomization)[a]**	**Period 1 (MRI scan)**	**Period 2 (Post-MRI Recovery)[b]**	**24-Hour (±2 hours)[c]**	**28-Day (+3 days)**
Informed consent	X				
Subject Number assigned	X				
Demography	X				
Medical history	X				
Inclusion/Exclusion criteria	X	X			
Physical examination[d]	X				
Contraception check[e]	X				X
Vital signs[f]	X	X	X		
$EtCO_2$[g]		X			
Rhythm strip (12-lead ECG if needed)[h]	X				
Laboratory: Pregnancy test[i]		X			
Randomization		X			
Peripheral IV placement[j]		X			
MRI scan[j]		X			
Cardiac telemetry[h]		X	X		
PSSS[k]		X			
Study treatment[l]		X			
Propofol (as needed)[l]		X			
Supplemental IV fluids[l]		X			
Modified Aldrete Score and PAED[m]			X		
CCI [redacted]			[redacted]		
AEs/SAEs[n]	X	→	→	→	X
Prior/Concomitant Treatments[o]	X	→	→	→	X

Abbreviations: → = continues; AE = adverse event; ECG = electrocardiogram; $EtCO_2$ = end-tidal carbon dioxide; IV = intravenous; MRI = magnetic resonance imaging; PAED = Pediatric Anesthesia Emergence Delirium Scale; PSSS = Pediatric Sedation State Scale; SAE = serious adverse event

a. Signed informed consent and age-appropriate assent must be obtained prior to conducting any tests, assessments or procedures. All Screening tests, assessments and procedure results must be received and reviewed by study site personnel prior to randomization. All inclusion criteria must be met and

Study Visit Identifier	Screen	Day 1 (Day of MRI scan)		Day 2 Follow-up	Day 29 Long-term Follow-up
Study Visit Scheduling/Window	Screening (up to 3 days before-randomization)[a]	Period 1 (MRI scan)	Period 2 (Post-MRI Recovery)[b]	24-Hour (±2 hours)[c]	28-Day (+3 days)

all exclusion criteria must not be met. The Screening Visit may occur on or up to 3 days before Day 1.

b. Subjects must be monitored per protocol requirements for a minimum of 1 hour; this must occur in a post-procedure recovery area such as a post-anesthesia care unit (PACU), recovery room or other hospital area where the required monitoring can be achieved. After 1 hour, subjects will meet criteria to leave this area when the subject attains a minimum Modified Aldrete Score of 9, is tolerating oral fluids and if applicable, any institution-specific discharge criteria have been met.

c. The Day 2 Follow-up visit will be completed 24 hours (±2 hours) after discontinuation of dexmedetomidine (DEX). Contact with the subject or parent/legal guardian may be done via a phone call.

d. Physical examination will include evaluation of general appearance, head, ears, eyes, nose, mouth, throat, neck, lungs, heart, abdomen, musculoskeletal, extremities, skin, lymph node and a neurological assessment.

e. The investigator must assess and document in the source if the subject is biologically capable of having/fathering children and if the subject is sexually active, continues to be sexually active or has become sexually active. If yes, their method of contraception and confirmation of its consistent and correct use must also be documented in the source documents.

f. Vital signs will include height (or length), weight, temperature, heart rate, respiratory rate, saturation of peripheral oxygen (SpO_2) and blood pressure including mean arterial pressure (MAP). Measurements should be obtained with the subject in a supine position as much as possible.

- Height will only be measured at Screening.
- Weight will only be measured at Screening and Day 1 Period 1 before randomization. If Screening and Day 1 occur on the same day, the weight does not need to be repeated.
- Height and weight values will be rounded to 1 decimal place (the nearest tenth) for calculations and documentation. If the second number to the right of the decimal point (the hundredths) is 4 or less, remove all numbers to the right of the tenths place. If the hundredths number is 5 or greater, add 1 to the number in the **tenths** place, and then remove all numbers to the right of the tenths place.
- Body temperature will be measured at Screening, at Day 1 Period 1 prior to randomization and during Day 1 Period 2 both when the subject arrives in the post-procedure recovery area and when they meet the criteria to leave this area. If Screening and Day 1 occur on the same day, the temperature does not need to be repeated at Day 1 Period 1 prior to randomization but would need to be obtained on Day 1 Period 2 in addition to Screening.
- Blood pressure, MAP, heart rate, respiratory rate and SpO_2 will be measured at Screening, within approximately 5 minutes before the loading dose and then every 5 (±1) minutes once the loading dose has started until the end of the MRI scan. The measurements obtained just before the loading dose will be considered the Baseline values for analysis purposes.
- On Day 1 Period 2, blood pressure including MAP, heart rate, respiratory rate and SpO_2 will be measured upon arrival in the post-procedure recovery area and then every 5 (±1) minutes for the first 15 minutes, and every 15 (±5) minutes for at least 1 hour until the subject attains a minimum

Study Visit Identifier	Screen	Day 1 (Day of MRI scan)		Day 2 Follow-up	Day 29 Long-term Follow-up
Study Visit Scheduling/Window	Screening (up to 3 days before-randomization)[a]	Period 1 (MRI scan)	Period 2 (Post-MRI Recovery)[b]	24-Hour (±2 hours)[c]	28-Day (+3 days)

Modified Aldrete Score of 9, is tolerating oral fluids and any institution-specific discharge criteria as applicable have been met.

- Heart rate, respiratory rate and SpO_2, as well as blood pressure where available, will also be monitored between scheduled readings either per site equipment monitoring standards or more frequently as deemed clinically necessary from the start of the study treatment loading dose through the post-MRI recovery period. If heart rate decreases >20% from Baseline and is outside the normal range, a blood pressure measurement including MAP should be repeated at approximately 2-minute intervals until the heart rate returns to the normal range. If systolic blood pressure decreases ≥30% from Baseline and is outside the normal range, a blood pressure measurement including MAP should be checked approximately 1 minute later. If the systolic blood pressure remains outside the normal range, measurements should be repeated at approximately 2-minute intervals until the systolic blood pressure returns to the normal range. Normal ranges are provided in Appendix 8, Normal Ranges by Age (Nelson Textbook of Pediatrics, 20th Ed, 2016). Baseline values are those obtained at Day 1 Period 1 within approximately 5 minutes prior to the start of the DEX loading dose.

g. Nasal cannula capnography will be used to monitor $EtCO_2$ concentrations from the start of the study treatment loading dose through the MRI scan. $EtCO_2$ data will not be collected on a CRF.

h. A 2-minute rhythm strip will be obtained at Screening, and a 12-lead ECG will be performed if clinically significant abnormalities are noted. If a site does not have the capability to obtain a hard copy rhythm strip, the 12-lead ECG may be performed in lieu of the rhythm strip. Subjects with a known history of cardiac disease will be required to have a 12-lead ECG performed at Screening. Cardiac telemetry monitoring is required beginning just prior to the start of the study treatment loading dose and continuing through the post-MRI recovery period.

i. For all female subjects of child-bearing potential, a urine dipstick or whole-blood qualitative human chorionic gonadotropin (hCG) pregnancy test that can be performed at the bedside will be performed on Day 1 Period 1. Serum qualitative or quantitative hCG pregnancy tests are not permitted. A negative pregnancy result is required before the subject may be randomized. Subjects with an indeterminate or positive test result may not randomize in the study. Please refer to Section 7.1 Pregnancy Testing for details.

j. DEX must be administered through a peripheral IV line that is not a central catheter such as a subclavian or peripherally inserted central catheter (PICC) line. The MRI scan may commence once the subject has achieved an adequate sedation level in the investigator's clinical judgment. The target sedation level is indicated by a Pediatric Sedation State Scale (PSSS) score of 2. During subject sedation, facilities for maintenance of a patent airway, provision of artificial ventilation, administration of supplemental oxygen and cardiovascular resuscitation must be immediately available. Site personnel trained in the use of resuscitative drugs and emergency equipment and skilled in airway management must be available at all times during subject sedation.

k. The PSSS sedation ratings will be 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.

l. After all Screening and Day 1 assessments have been completed and reviewed, subject has been confirmed as meeting entry criteria and has been randomized, study treatment will be administered as a 2-stage intravenous infusion to be started just prior to the start of the MRI scan. Immediately prior to the scan, a loading dose of dexmedetomidine (DEX) will be administered over a period of 10 minutes. Then a continuous maintenance dose infusion

Study Visit Identifier	Screen	Day 1 (Day of MRI scan)		Day 2 Follow-up	Day 29 Long-term Follow-up
Study Visit Scheduling/Window	Screening (up to 3 days before-randomization)[a]	Period 1 (MRI scan)	Period 2 (Post-MRI Recovery)[b]	24-Hour (±2 hours)[c]	28-Day (+3 days)

of DEX will be started that will continue for the duration of the scan. Concomitant PRO may be administered starting 5 minutes following the start of the DEX maintenance infusion to ensure that an adequate level of sedation is achieved prior to and throughout the scan. Subjects will also be required to receive supplemental IV fluids during the administration of DEX. The use, type and rate of maintenance fluid administration following discontinuation of DEX will be at site discretion. Please refer to Section 5, Study Treatment, for details.

m. The Modified Aldrete Score will be performed on arrival at the post-procedure recovery area and every 15 (±5) minutes until the subject meets criteria to leave that area. The PAED will be performed after the subject awakens following arrival at the post-procedure recovery area and every 15 (±5) minutes until the subject meets criteria to leave that area. If any total score on the PAED is 10 or greater, the subject should be evaluated for emergence delirium, treated as appropriate and the PAED assessment frequency should be increased to every 5 (±1) minutes until the PAED score is below 10 or the subject leaves that area. CCI [redacted]

n. Adverse events (AEs) and serious adverse events (SAEs) will be collected from the time the informed consent is obtained through the Day 29 Long-term Follow-up Visit or final visit prior to the Day 29 Long-term Follow-up Visit as appropriate. See Section 8.1.4, Time Period for Collecting AE/SAE Information, for further details. The Day 29 Long-term Follow-up Visit is a telephone contact visit to elicit contraception and AE/SAE information only. SAE information must be reported to Pfizer per Section 8.1.4.1 Reporting SAEs to Pfizer Safety.

o. Prior medications and non-pharmacologic therapies will be collected for the 4-week period before randomization. Concomitant treatments and non-pharmacologic therapies will be collected from randomization through the Day 29 Long-term Follow-up Visit as described in Section 5, Study Treatments.

1. INTRODUCTION

The present study is being conducted by Pfizer, Inc under the Pediatric Research Equity Act (PREA) and is a Phase 3/4 randomized, double-blind, dose-ranging study of the safety and efficacy of dexmedetomidine (DEX) used with propofol (PRO) for procedural sedation of pediatric subjects ≥1 month to <17 years of age undergoing magnetic resonance imaging (MRI) scans.

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

1.1. Mechanism of Action and Indication

DEX is a highly selective α2-adrenergic agonist that is being investigated for use in procedural sedation in pediatric subjects undergoing MRI requiring moderate to deep sedation. DEX is currently approved for sedation of initially intubated and mechanically ventilated adults during treatment in an intensive care setting and for procedural sedation of adults.

The effects of DEX are mediated via adrenoreceptors in both the central and peripheral nervous systems. Owing to the wide distribution of adrenergic receptors, DEX has effects across multiple organ systems and in some cases, multiple effects on a single organ system. For example, DEX has a dual effect on the cardiovascular system. Upon administration DEX has a transient peripheral effect mediated through its stimulation of α2- receptors on vascular smooth muscle causing an increase in blood pressure and a reflex decrease in heart rate. In the heart, the dominant effect of DEX is to induce bradycardia─ mediated through vagal stimulation and a decrease in tachycardia as DEX blocks the cardio accelerator nerves. In children, large doses of dexmedetomidine have been shown to cause peripheral vasoconstriction, leading to transient systemic hypertension, whereas low doses can cause central sympatholysis, leading to systemic hypotension.[1-4]

The sedative and anxiolytic effects result primarily from activity in the locus ceruleus of the brain stem where stimulation of the α2-adrenergic receptors inhibits norepinephrine release, resulting in increased firing of inhibitory neurons. In the dorsal horn of the spinal cord, DEX modulates the release of substance P which produces its analgesic effects.[5] The α2-adrenergic agonist action of DEX results in mild to moderate analgesia, sedation, anxiolysis, diuresis, peripheral and central effects on the cardiovascular system, and mild inhibition of insulin release and platelet aggregation.[6]

In healthy subjects, DEX caused dose-dependent decreases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) and a slowed heart rate but did not alter respiratory rate or oxygen saturation at recommended dosages.[6,7,8]

1.2. Approval History and PREA

In December 1999, Precedex (developed by Hospira Inc.) received regulatory approval in the United States for sedation of initially intubated and mechanically ventilated adults in an intensive care unit (ICU) setting for up to 24 hours. In October 2008 DEX was approved for

use in non-intubated adults requiring sedation prior to and/or during surgical and other procedures.

In 2007 the FDA issued a PediatricWritten Request (PWR) in ICU sedation. In response, 6 studies were conducted, and the results submitted to the FDA. In March 2013, following 2 amendments (December 2010 and August 2011), the FDA granted Pediatric Exclusivity for Precedex, based on the fulfillment of the requirements of the PWR. However, based on the FDA's assessment of insufficient proof of efficacy and safety, they did not accept the results of the PWR studies as adequate to support the approval of an indication for Precedex in pediatric ICU sedation.

In 2008 following the approval of DEX for procedural sedation in adults, a PREA request was issued to conduct a clinical study in pediatric subjects receiving DEX for procedural sedation. In response, study DEX 10-16, entitled Phase IV, Open Label, Safety Study Evaluating the Use of Dexmedetomidine in Pediatric Subjects Undergoing Procedure-Type Sedation was conducted to fulfill the PREA requirement. The objective of the DEX 10-16 study was to evaluate safety; this study was not intended to support an indication for the use of DEX in pediatric procedural sedation (PPS). The DEX 10-16 study ultimately did not fulfill the PREA requirement, and FDA advised consultation with clinical experts in PPS to inform the design of a new study and ensure that the study reflected the way DEX was used in clinical practice (ie, with regard to dose selection and rationale, types of procedures, and use of concomitant sedative drugs).

1.2.1. Study DEX 10-16

DEX 10-16 was an open-labeled, single-arm, multi-center study designed to evaluate the safety of DEX in pediatric subjects ages ≥28 weeks to <17 years old who required non-intubated moderate to deep sedation (NI-MDS) for procedures lasting at least 30 minutes and falling into 1 of the following 3 procedural groups:

- Non-invasive diagnostic/therapeutic procedures including ultrasound (U/S), computed tomography (CT) scans, MRI, cardiac catheterization or transthoracic echocardiogram (TTE).

- Minimally invasive diagnostic/therapeutic procedures such as procedures performed under U/S or CT guidance (eg, U/S or CT-guided solid organ biopsy), and routine myocardial biopsies in cardiac transplant recipients.

- Surgical procedures including small surgical procedures (eg, excisions, biopsies) and dental procedures (eg, extractions, pulpectomy, pediatric rehabilitation dental procedures, fillings, and crowns).

Dosing of DEX was based on age: subjects aged ≥28 weeks' gestational age to <1 month postnatal (n=1) received a 0.1 microgram/kilogram (mcg/kg) loading dose over 10 minutes and a 0.05 - 0.2 mcg/kg/hour infusion; subjects aged 1 month to <17 years (n=90) received a 1 mcg/kg loading dose over 10 minutes and a 0.2 - 2 mcg/kg/hour infusion.

Although DEX 10-16 was initially designed to assess safety only, based on feedback from the FDA, the study was revised to incorporate assessments of efficacy.

The primary efficacy endpoint of DEX 10-16 was the rate of successful sedation. This was a composite endpoint consisting of the following 3 criteria, all of which had to be satisfied for a sedation to be considered a success:

- Subject had adequate level of sedation (University of Michigan Sedation Scale [UMSS] score of 1 to 3 or a Neonatal Pain, Agitation and Sedation Scale [N-PASS] score of -5 to -2) at least 80% of the time the subject was given the study drug.
- Subject successfully completed the procedure without rescue medication (midazolam).
- Subject did not need artificial ventilation or intervention to restore baseline or normal hemodynamic status.

The primary safety endpoint of DEX 10-16 was the incidence of treatment-emergent adverse events (TEAEs).

The study enrolled 91 subjects, of whom 90 subjects were included in the safety evaluable population and 78 in the efficacy evaluable population.

1.2.1.1. Study DEX 10-16 Study Results

DEX 10-16 demonstrated that DEX was generally safe and well tolerated in pediatric subjects who were undergoing procedural sedation. The most common TEAE was respiratory depression (62%) which was pre-defined in the protocol as the presence of either absolute or relative thresholds for respiratory rate and saturation of peripheral oxygen (SpO2) changes. None of the events of respiratory depression required medical intervention or resulted in a subject discontinuing from the study. The other common TEAEs were hypotension (37%) and bradycardia (4.4%).[9]

Based on the 3 criteria comprising the primary efficacy endpoint, the study failed to demonstrate efficacy. The majority of subjects in all 3 procedural groups required rescue midazolam for adequate sedation. Only 2 subjects met the criteria for successful sedation; both were in the non-invasive procedure group. Notably, the need for rescue sedation and incidence of AEs increased with increasingly invasive/painful procedures. More subjects in the non-invasive procedures group (primarily subjects undergoing imaging studies) were adequately sedated compared to subjects in the minimally invasive or surgical procedures groups.

1.2.2. DEX Expert Advisory Committee

In preparation for the current protocol, Pfizer assembled a team of 5 nationally and internationally recognized Clinical Experts in the field of pediatric sedation and met with them for advice in designing a study based on current clinical practice for the use of DEX for PPS. As a result of that meeting and subsequent communication with the Advisory

Committee, the procedures for study, dose range and concomitant sedation drugs for this study were determined.

1.2.2.1. Imaging Procedures

The Clinical Experts recommended that Pfizer include only MRI/non-invasive imaging procedures for this study because approximately 80% of DEX used in pediatric procedural sedation is for imaging procedures. The predominant use of DEX for sedation for imaging procedures (MRI in particular) is also strongly supported by the the literature.[10,11,12]

1.2.2.2. Dose Selection

Pharmacokinetic (PK) data from adults undergoing procedural sedation with DEX is not available and only limited PK data is available for pediatric subjects.[13] Additionally, no PK/Pharmacodynamic (PD) model has been established to guide dose selection in pediatric subjects undergoing procedural sedation with DEX. In the absence of PK and modeling data to guide dose selection for this study, the selection of the DEX dosing regimens was based on consideration of the following:

1. The recommended DEX dose for procedural sedation in adults.
2. The dosing experience and results of the previous pediatric procedural sedation study DEX 10-16.
3. The available PK data in adult and pediatric ICU subjects, as well as simulated PK profiles of DEX at the projected doses in pediatric procedural sedation subjects based on a population PK model developed from the ICU pediatric subjects (Appendix 2).
4. The published literature in similar patient populations undergoing similar non-invasive imaging procedures.
5. Reports of dose-related effects of DEX on required concomitant anesthesia.
6. Clinical expert advisor recommendations.

The doses selected for this study are shown below:

Blinded dosing for subjects ≥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

Blinded dosing for subjects ≥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

Lower loading doses were selected for subjects <2 years old compared to subjects from 2 to <17 years of age because of a potential increased risk of respiratory insufficiency leading to hypoxia and bradycardia in newborns and infants treated with high doses of DEX.[14]

The clinical expert advisory board unanimously agreed that the dosing regimen used in the DEX 10-16 study does not reflect current clinical usage. The DEX doses used in children in practice today are higher than the doses administered in the DEX 10-16 study and higher than the doses specified for adults in the current label.

Since the approval of DEX for adult procedural sedation in 2008, there have been numerous publications on the use of DEX for PPS, chiefly for non-invasive procedures such as MRI, CT, nuclear medicine studies, and electroencephalograms (EEG). A review of this literature reveals that the range of loading and maintenance doses used in pediatric subjects is frequently higher than the recommended adult dose. In addition, there has been a progressive increase in the doses used over time.

Mason et al. reported on 747 consecutive pediatric patients who received DEX for MRI sedation.[15] Between April 2005 and April 2007 the loading dose of DEX was increased from 2 to 3 mcg/kg, and the maintenance infusion rate increased from 1 mcg/kg/hour to 1.5 to 2 mcg/kg/hour. During this time the success rate of sedation with DEX alone increased from 91.8% to 97.6% of patients being able to complete the imaging study. Similarly, Siddappa et al reported on the successful use of high-dose DEX (2 mcg/kg loading dose followed by 1 mcg/kg/hour infusion) for sedation during MRI.[11] The safety profile of DEX at these higher doses was found to be acceptable and was characterized in multiple studies by a modest decrease in heart rate and blood pressure that typically did not require intervention.[14]

Co-administration of DEX with other sedatives such as ketamine, midazolam, or PRO is also common; about 67% of cases in the recent analysis of the DEX database by Sulton et al. utilized concomitant sedatives such as midazolam or ketamine.[10] In addition, DEX has been reported to exert a dose-sparing effect on the requirement for concomitant opioids and sedatives.[16,17] The reduced need for concomitant sedatives is significant, given increasing concerns regarding potential neurotoxic effects of anesthetics in developing children.[18,19]

The doses selected for this study were based on the combined information from the above sources and input from clinical experts. The selected doses range from a minimally effective low dose to maximum doses, which are representative of current clinical usage.

It is anticipated that the proportion of subjects adequately sedated at the lowest dose level (0.5 mcg/kg loading dose and 0.5 mcg/kg/hour maintenance dose) will be low. As reported by Berkenbosch et al., initial use of a 0.5 mcg/kg induction and 0.5 mcg/kg/hour maintenance dose regimen failed to achieve adequate sedation and prevent patient movement in most children undergoing MRI scans, leading subsequently to the use of higher DEX doses.[20] The middle dose level chosen for this study is comparable to the approved dose for adult procedural sedation and the dose utilized in the original Hospira pediatric trial (DEX 10-16), in which approximately 30% of subjects undergoing MRI did not require supplemental midazolam. The high doses were chosen to be more representative of current practice, and it is expected that up to 70-80% of subjects who receive this dose level will not require supplemental anesthetic to achieve adequate sedation.[15] Across the dose range to be studied, it is anticipated that increasing dose levels of DEX will be associated with a decreasing requirement for a concomitant sedative, and with an increasing proportion of subjects who are able to complete the procedure with DEX alone.

Although there are very limited PK data available for DEX used for procedural sedation, the PK of DEX has been well characterized in adults and in pediatric ICU subjects. DEX undergoes extensive hepatic metabolism to inactive metabolites, with 85% undergoing glucuronidation by UDP-glucuronyltransferase (UGT) and 15% by cytochrome P450 2A6. In adults, following intravenous (IV) administration, DEX exhibits a rapid distribution phase with a distribution half-life (t½) of approximately 6 minutes; a terminal elimination t½ of approximately 2 hours; a steady-state volume of distribution (Vdss) of approximately 118 L, and an estimated clearance of approximately 39 L/hour. In adults, DEX exhibits linear PK in the dosage range of 0.2 to 0.7 mcg/kg/hour when administered by IV infusion for up to 24 hours.[21,22]

Based on the results from 5 clinical studies (W98-266, CHOP, DEX 08-01, DEX 08-09, and DEX 11-01) in pediatric ICU subjects ranging in age from 1 month to 17 years, the median weight-adjusted DEX clearance values were between 0.79 and 1.32 L/hour/kg and the median weight-adjusted volume of distribution (Vd) values, between 2.09 and 3.64 L/kg. DEX exhibits linear PK across the dosage range of 0.2 to 2 mcg/kg/hour studied in pediatric ICU subjects when administered by IV infusion for up to 24 hours. Hence, the exposure of DEX in this study is expected to be dose-proportional within the proposed DEX dosage range of 0.5 to 2 mcg/kg/hour in PPS subjects.

1.2.2.2.1. Loading Dose Infusion Duration

The Precedex United States Package Insert (USPI) recommends a loading dose of 1 mcg/kg infused over 10 minutes for adults (DEX is not approved for pediatric use). The pediatric ICU sedation studies used a 10-minute interval for infusion of the DEX loading dose. However, there are some literature reports of PPS studies that infused the DEX loading dose over ≤5 minutes. Some members of our clinical expert advisory committee also use an infusion rate of ≤5 minutes for PPS. This practice of shortening the duration of the loading dose infusion is employed primarily at tertiary care hospitals and by very experienced providers with specialized interest and/or training in using DEX for PPS. However, while there is little published data on the safety and tolerability of different infusion duration times,

a shorter duration may be associated with increased AEs. Therefore, this study will use the more conservative 10-minute infusion interval for the DEX loading dose, which is consistent with the current USPI as recommended for adults.

1.2.2.3. Concomitant Sedative Drugs

The Clinical Experts emphasized that in practice, DEX is usually used in combination with other sedatives and analgesics (ie, midazolam, PRO, ketamine, morphine, or fentanyl).[10]

For an MRI to be successful the subject must remain motionless during image capture and therefore in young children deep sedation is necessary. While multiple sedative drug regimens have been used to achieve deep sedation for MRI studies, PRO has become a commonly used drug because it has a short induction and recovery time and can be titrated easily to the required sedation level.[23,24] In this study, PRO will be used as a rescue sedative in subjects who are not sufficiently sedated by DEX alone.

1.2.2.4. Summary of Study Design

This study design is based on the comments received in the FDA's complete response letter (CRL) of August 2016 and the recommendations of the Clinical Expert advisory committee. The study is designed to meet the post-marketing study requirements (PMR 1772-1) to fulfill the PREA requirements and to investigate the safety and efficacy of DEX for pediatric procedural sedation.

This clinical trial will be a randomized, double-blind, fixed dose-ranging study of the efficacy and safety of DEX, when used with PRO administered as needed, for procedural sedation of pediatric subjects ≥1 month to <17 years of age undergoing diagnostic magnetic resonance imaging (MRI) scans.

1.3. Safety Data

1.3.1. Clinical Trial Safety Data Base

The legacy Hospira clinical safety data base for DEX pediatric studies contains safety information on 319 pediatric subjects participating in 6 studies conducted on the use of DEX for ICU pediatric sedation and 90 subjects receiving DEX for PPS in DEX 10-16.

1.3.1.1. Safety Data from Pediatric ICU Sedation Studies

In support of the Pediatric Written Request for DEX for the indication of sedation in initially intubated and mechanically ventilated pediatric ICU (PICU) subjects, Hospira completed 6 pediatric clinical studies with a total of 319 subjects aged 28 weeks to <17 yr. In these studies, the loading dose was given over 10 minutes and the maintenance doses were as follows:

- 28 weeks gestational age to <1 month chronological age: loading dose of 0.05 - 0.2 mcg/kg and maintenance dose of 0.05 - 0.2 mcg/kg/hour.

- 1 month to ≤16 years of age: loading dose of 0.25 - 0.5 mcg/kg and maintenance dose of 0.2 - 0.5 mcg/kg/hour.

- 1 month to ≤16 years of age: loading dose 0.5 - 1 mcg/kg and maintenance dose of 0.5 - 2 mcg/kg/hour.

Adverse events occurring between the start of the DEX infusion and up to 24 hours after its discontinuation (study end) were considered TEAEs. Among the 319 pediatric subjects in the integrated safety population, 203(63.3%) had 1 or more TEAEs, 2.5% had severe TEAEs, and 50 subjects (15.7%) had one or more drug-related TEAEs. Nine subjects (2.8%) had 1 or more treatment emergent serious adverse events (SAEs); 4 subjects had treatment-emergent SAEs that were considered drug-related. Thirteen subjects (4.1%) had TEAEs leading to discontinuation; the incidence of any single TEAE leading to discontinuation was low, ranging from 0.3 to 0.6%. No single TEAE led to discontinuation in more than two subjects, and no subjects died as a result of a TEAE.

Most TEAEs in the PICU sedation studies were mild in severity (2.5% were considered severe). No subject had a TEAE resulting in death. The incidences of discontinuations due to TEAEs was low (4.1%), and no single TEAE leading to discontinuation occurred in more than two subjects. The incidence of treatment-emergent SAEs leading to discontinuation was also low (1.3%), and none of the treatment-emergent SAE leading to discontinuation occurred in more than one subject.

The most common TEAEs were hypertension (43 subjects, 13.5%), hyperglycemia (36 subjects, 11.6%, with no hyperglycemia considered related to drug), hypotension (32 subjects, 10.1%), hypokalemia (28 subjects, 8.8%), pyrexia (26 subjects 8.2%), and vomiting (16 subjects, 5.0%).

Based on the known mechanism of action of DEX and its adverse event profile in adults, certain adverse events were considered “adverse events of special interest”. These adverse events included bradycardia, tachycardia, hypotension, diastolic hypotension, and systolic hypertension. The majority of AEs of special interest did not require medical intervention, which was defined as any action taken in response to the AE and included decreasing the infusion rate of DEX, re-positioning the patient and/or treatment with fluids, medications, or procedures. The Incidence of AEs of Special Interest and the incidence of these events requiring medical intervention are shown below:

The Incidence of AEs of Special Interest vs. Incidence of AEs of Special Interest Receiving Medical Attention in an Integrated Pediatric Population During ICU Sedation <24 Hours

Adverse event	**Subjects with AEs of special interest N=319 n (%)**	**Subjects receiving medical intervention N=319 n (%)**
Bradycardia	11 (3.4)	3 (0.9)

Adverse event	Subjects with AEs of special interest N=319 n (%)	Subjects receiving medical intervention N=319 n (%)
Tachycardia	12 (3.8)	1 (0.3)
Hypertension	43 (13.5)	14 (4.4)
Hypotension	34 (10.7)	11 (3.4)

The changes in vital signs (blood pressure [BP] and heart rate [HR]) across the PICU sedation studies were predictable given DEX's mechanism of action and were generally manageable. Additionally, DEX had no clinically meaningful effect on hematology or serum chemistry analytes.

Overall, considering the underlying medical condition of the pediatric subjects upon enrollment (subjects had to be intubated and mechanically ventilated to qualify for the studies), DEX appeared to be generally safe and well-tolerated in the sedation of initially intubated and mechanically ventilated PICU subjects. The TEAEs that occurred were generally consistent with the known AE profile of DEX in the adult population.[25]

1.3.1.2. Safety Data from Pediatric Procedural Sedation Study DEX 10-16

As discussed in Section 1.2.1.1, study DEX 10-16 demonstrated that DEX was generally safe and consistent with the known safety profile of DEX in adults.[26] Adverse events of special interest were AEs of bradycardia, tachycardia, hypotension, hypertension, hypoxia and respiratory depression based on protocol-defined vital signs limits. The frequency of subjects experiencing a TEAE and TEAE of special interest in subjects undergoing non-invasive diagnostic/therapeutic procedures were 32 (69.6%) and 30 (65.2%). With few exceptions, all TEAEs were TEAEs of special interest. The commonly reported treatment-related TEAEs (reported in ≥2 subjects) were hypotension in 30 subjects (33.3%), respiratory depression in 19 subjects (21.1%), bradycardia in 3 subjects (3.3%), and vomiting, BP systolic decreased, headache and hypoxia in 2 subjects each (2.2%).

The increased frequency of TEAEs of bradypnea and hypotension was noted with more invasive procedures, and with increased use of rescue sedation and analgesia. As noted by Jooste et al, the high incidence (62%) of the protocol-defined decrease in respiratory rate of >30% from baseline, was not viewed as being clinically significant and represents a normal decrease in the respiratory rate of a child who is well-sedated in pediatric subjects undergoing procedural sedation. All of the AEs reported were in calmly sedated children compared with that of a child in a relatively anxious pre-sedation state.[9] There were 2 events of a >10% decrease in the saturation of peripheral oxygen (SpO_2) from baseline that resolved quickly, and none of the subjects in DEX 10-16 required mechanical ventilation either during or post study drug infusion.

There was 1 treatment-emergent SAE of syncope reported in this study. This event was reported. The SAE of syncope was assessed as probably not related to DEX and resolved without treatment.

1.4. Safety Summary

Based on the safety data from the pediatric ICU sedation studies, the DEX 10-16 study in PPS, and the published literature, DEX is generally safe and well tolerated in pediatric subjects. The most common TEAEs - hypotension, respiratory depression, and bradycardia, are well understood based on the drugs mechanism of action, are generally mild, and generally resolve without medical intervention.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of DEX may be found in the Investigator Brochure (IB), which is the single reference safety document (SRSD) for this study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PRO may be found in the United States package insert [(USPI], which is the SRSD for this study. Individual countries may also reference their local package insert for additional country-specific information on PRO.

2. STUDY OBJECTIVES AND ENDPOINTS

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 do 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 do not require concomitant PRO to complete the 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 do 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 do not require concomitant PRO to complete the MRI.
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 do 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 do 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 receive 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.
CCI [redacted]	[redacted]
[redacted]	[redacted]
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. • 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 SBP, DBP, mean arterial pressure (MAP), 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 of bradypnea, hypoxia and apnea. • Incidence of protocol-specified cardiac adverse events of hypotension, hypertension and bradycardia. • Incidence of protocol-specified adverse event of paradoxical agitation reaction. • Incidence of protocol-specified adverse events of bradypnea, hypoxia, apnea, hypotension, hypertension, bradycardia and paradoxical agitation reaction requiring intervention. • Incidence of DEX withdrawal-related adverse events after discontinuation of DEX infusion.
Safety Assessments	• Exposure to study drug (total dose of study drug received and the duration of study drug infusion). • Adverse Events (AEs). • Cardiac telemetry. • Vital signs (HR, blood pressure [DBP, SBP and MAP], RR, temperature, SpO_2), end-tidal carbon dioxide ($EtCO_2$) and body weight. • Prior and concomitant medications. • Pediatric Anesthesia Emergence Delirium Scale (PAED).

3. STUDY DESIGN

This is 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 subjects ≥1 month to <17 years of age undergoing MRI scans. The sponsor, subject and investigator will be blinded to the dose of DEX.

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

All eligible subjects will receive double-blind treatment where one of 3 dose levels of DEX will be administered. Following completion of required procedures before randomization at the Day 1 Visit, subjects meeting entry criteria will be randomly assigned to a Low, Middle or High dose level group (actual dose dependent on age) in a 1:1:1 ratio.

Treatment will be initiated just prior to the start of the MRI scan and will continue during Period 1 (MRI scan). Subjects will first receive a DEX loading dose administered over 10 minutes. Following completion of the loading dose, the maintenance infusion of DEX will be started. The subject's level of sedation will be assessed using the Pediatric Sedation State Scale (PSSS) at 5-minute intervals throughout the drug infusion and MRI scan. If an adequate level of sedation is not achieved as assessed by the investigator (eg, if the subject moves) within 5 minutes after the DEX maintenance infusion has been started, concomitant PRO may be given to ensure that an adequate sedation level is achieved and maintained for completion of the scan. The target sedation level is indicated by a PSSS score of 2 (ie, patient is quiet [asleep or awake], not moving during procedure, has no frown [or brow furrow] indicating pain or anxiety and no verbalization of any complaint).[27]

Once the subject has achieved an adequate sedation level per principal investigator (PI) clinical judgment, the MRI scan can commence. Sedation with DEX and if required, concomitant PRO, shall continue through completion of the MRI scan to maintain the subject at an adequate sedation level per PI clinical judgment.

Subjects will also be administered supplemental IV fluids throughout the DEX infusion at a maintenance rate per Section 5.10.1 Required Treatments. Please refer to the Investigational Product Manual (IP Manual) for the list of permitted IV fluids that may be used. The use, type and rate of maintenance fluid administration following discontinuation of the DEX infusion will be at the site's discretion.

During subject sedation, facilities for maintenance of a patent airway, provision of artificial ventilation, administration of supplemental oxygen and cardiovascular resuscitation must be immediately available. Site personnel trained in the use of resuscitative drugs and emergency equipment and skilled in airway management must be available at all times during subject sedation.

The DEX infusion should not be discontinued until confirmation that the MRI is complete has been received and DEX must be discontinued prior to the subject being transferred to the post-procedural recovery area. Period 2 (post-MRI recovery) begins at the conclusion of the MRI scan.

The study will be conducted using the manufactured strength of DEX 200 mcg/2 mL, diluted to a concentration directed by the Investigational Product Manual (IP Manual) based on each subject's treatment group assignment.

3.1. Approximate Duration of Subject Participation

Subjects will participate in the study for ~4 weeks.

3.2. Approximate Number of Subjects

A sufficient number of subjects will be screened to randomize approximately 120 subjects (40 subjects per dose level) who will participate in the study. The numbers of enrolled subjects are not pre-specified for each participating country. Enrollment is competitive and

will depend on the capabilities of each site. Subjects who withdraw from the study will not be replaced.

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

- Age Cohort ≥1 month to <2 years:

  This age cohort should have an even distribution of subjects between the ages of 1 month to <2 years on Day 1 within each dose group:

  - Approximately 10 subjects aged ≥1 month to <1 year in each dose group.
  - Approximately 10 subjects aged ≥1 year to <2 years in each dose group.

- Age Cohort ≥2 years to <17 years:

  This age cohort should have an even distribution of subjects between the ages of 2 years to <12 years on Day 1 within each dose group:

  - Approximately 8 subjects aged ≥2 years to <6 years in each dose group.
  - Approximately 8 subjects aged ≥6 years to <12 years in each dose group.
  - Approximately 4, but no more than 5 subjects aged ≥12 years to <17 years in each dose group.

- All age cohorts can be enrolled in parallel.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

a. Are pre-menarche;

b. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological

cause; status may be confirmed with a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

c. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

d. Have medically confirmed ovarian failure.

All other female subjects who have experienced menarche (including female subjects with tubal ligations) are considered to be of childbearing potential.

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

4.1. Inclusion Criteria at Screening

Subjects must meet all the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject or a parent(s)/legal guardian has been informed of all pertinent aspects of the study. Assent will also be obtained where age-appropriate and according to state regulations.

2. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Male or female subject ≥1 month and <17 years of age on Day 1.

4. American Society of Anesthesiologists (ASA) Physical Status I, II or III. This assessment is to be performed by a medically qualified person and reviewed by the PI.

5. Requires non-intubated, spontaneous breathing, moderate to deep sedation (NI-MDS) for a magnetic resonance imaging (MRI) study with an intensivist, anesthesiologist or other proceduralist in attendance.

6. Duration of the MRI scan is expected to take at least 20 minutes but no more than 3 hours to complete.

7. Subjects must be willing and able to undergo placement of a peripheral IV catheter inserted specifically for this study. Existing IV catheters being used for another purpose (eg, administration of fluids, IV antibiotics etc.) must be used with the Sponsor provided Y-connector and 3-port connector. Existing IV tubing must not be used.

4.2. Inclusion Criteria on Day 1

Subjects must meet all the following inclusion criteria to be eligible for enrollment into the study:

1. All Screening inclusion criteria continue to apply as appropriate.

4.3. Exclusion Criteria at Screening

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

2. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation. This includes investigational medicinal products and investigational vaccines received outside of a clinical study such as coronavirus disease 2019 (COVID-19) vaccines that do not have emergency use authorization. Approved or Emergency Use Authorized medicinal products and vaccines are not considered investigational and do not fall into this category.

3. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4. Female subjects of childbearing potential who are sexually active who have not been using a highly effective method of contraception as outlined in this protocol during the 2 weeks prior to randomization.

5. Fertile male subjects and female subjects of childbearing potential who are sexually active and are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.

6. Weight at Screening is less than the 10th percentile of weight for age and sex or is greater than the 95th percentile of weight for age and sex (97th percentile in Japan) based on sponsor-provided growth charts.

7. Previous participation in this study or concurrent participation in any other interventional non-observational study.

8. Planned medical procedure during the MRI scan or post-MRI recovery period. Non-interventional/observational procedures are not exclusionary.

9. Craniofacial anomaly that could make it difficult to effectively establish a mask airway for positive pressure ventilation if needed.

10. Requires endotracheal intubation or laryngeal mask airway (LMA).

11. Neurological or psychiatric condition that in the opinion of the Investigator could confound reliable assessment of sedation score. Examples include but are not limited to cerebral palsy, autism, severe mental retardation, etc.

12. Other central nervous system (CNS) disease including an uncontrolled seizure disorder, any seizure activity within 1 week of Day 1, known history of or anticipated potential for increased intracranial pressure, and/or known psychiatric illness that could confound a normal response to sedatives. History of single childhood febrile seizure is not exclusionary.

13. Known Type I diabetes mellitus (DM), or insulin dependent Type II DM.

14. Known history of significant renal or liver disease.

15. Uncorrected hypothyroidism or hyperthyroidism or subjects whose thyroid function and medication regimen have been stable less than 1 month prior to Day 1.

16. Known hypersensitivity to DEX or PRO or any of the Diprivan® Injectable emulsion components.

17. Known allergy to eggs, egg products, soybeans or soybean products.

18. Subjects for whom PRO, opiates, benzodiazepines, DEX or other alpha-2 agonists are contraindicated.

19. Received general anesthesia within 7 days prior to the planned start of the investigational product administration.

20. Received treatment with an alpha-2 agonist or antagonist within 14 days prior to the planned start of the investigational product administration.

21. Received digoxin in the month prior to the planned start of the investigational product administration.

22. Known second- or third-degree heart block or clinically significant abnormal findings on the Screening rhythm strip or electrocardiogram (ECG) diagnostic of atrioventricular (AV) conduction block or sustained cardiac arrhythmia.

23. Symptomatic cardiac or respiratory disease that, in the Investigator's opinion, might increase the risk to the subject.

24. Requirement for an apnea monitor within the past 3 months, or moderate to severe Sleep Apnea Syndrome based on clinical history or sleep study.

25. SpO2 <93 % on room air.

26. A temperature (core or tympanic) ≥38.0° Centigrade.

27. Any other medication, condition or factor that, in the Investigator's opinion, might increase the risk to the subject.

28. Any subject that, in the Investigator's opinion, is exhibiting any behavior(s) or indication(s) that they may be under the influence of alcohol or drugs of abuse.

29. Heart rate values at Screening according to the respective age groups below based on the 10th centile data from the HR table in Appendix 7, HR and RR Centile Chart Cut-offs for Children from Birth to 18 Years of Age (Fleming et al, Lancet 2011). Subject can be reassessed after 5 minutes and can be considered for randomization if their heart rate increases above the criteria.

Exclusion Criteria for Heart Rate	
Age	**Heart Rate**
≥1 month to <3 months	<123 beats per minute (bpm)
≥3 months to <6 months	<120 bpm
≥6 months to <9 months	<114 bpm
≥9 months to <12 months	<109 bpm
≥12 months to <18 months	<103 bpm
≥18 months to <24 months	<98 bpm
≥2 year to <3 years	<92 bpm
≥3 years to <4 years	<86 bpm
≥4 years to <6 years	<81 bpm
≥6 years to <8 years	<74 bpm
≥8 years to <12 years	<67 bpm
≥12 years to <15 years	<62 bpm
≥15 years to <18 years	<58 bpm

30. Systolic blood pressure values at Screening according to the respective age groups below based on the BP data from the table in Appendix 8, Normal Vital Signs According to Age (Nelson Textbook of Pediatrics 20th Ed, 2016). Subject can be reassessed after 5 minutes and can be considered for randomization if their blood pressure does not meet the below criteria.

Exclusion Criteria for Systolic Blood Pressure	
Age	**SBP**
≥1 month to <3 months	<65 or >85 millimeters of mercury (mm Hg)
≥3 months to <6 months	<70 or >90 mm Hg
≥6 months to <1 year	<80 or >100 mm Hg
≥1 year to <3 years	<90 or >105 mm Hg
≥3 years to <6 years	<95 or >110 mm Hg
≥6 years to <12 years	<100 or >120 mm Hg
≥12 years to <17 years	<110 or >135 mm Hg

4.4. Exclusion Criteria on Day 1

Subjects with any of the following characteristics/conditions will not be included in the study:

1. All Screening exclusion criteria continue to apply as appropriate.

2. Pregnant female subjects (including those with an indeterminate or positive pregnancy test); breastfeeding female subjects.

3. Weight on Day 1 before randomization is less than the 10th percentile of weight for age and sex or is greater than the 95th percentile of weight for age and sex (97th percentile in Japan) based on sponsor-provided growth charts.

4. Exposed to DEX within 48 hours prior to the planned start of the investigational product administration.

5. Received an IV opioid within one hour, or oral/intra-muscular (PO/IM) opioid within 4 hours prior to the planned start of the investigational product administration.

6. Received any medication that has sedative or hypnotic properties within 4 hours prior to the planned start of the investigational product administration.

7. Received any pre-induction medication (ie, ketamine, chloral hydrate, benzodiazepines) within 4 hours prior to the planned start of the investigational product administration, other than planned gas induction to be administered via mask for placement of IV access as described in Section 5.10.2 Permitted Concomitant Treatments.

8. Received anti-depressant agents (eg, fluoxetine) during the 48-hour period prior to the planned start of the investigational product administration.

4.5. Lifestyle Requirements

4.5.1. Contraception

All fertile male subjects and female subjects who are of childbearing potential who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s),

must have been using a highly effective method of contraception consistently and correctly for at least 2 weeks prior to Day 1 and must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator or his or her designee will confirm that the subject has selected an appropriate method of contraception from the list of permitted contraception methods (see below). At time points indicated in the Schedule of Activities, the investigator or designee will instruct the subject of the need to use highly effective contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's chart. In addition, the investigator or designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.

All sexually active male subjects must agree to prevent potential transfer to and exposure of partner(s) to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 28 days after the last dose of investigational product.

4.6. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list *located in the supporting study documentation*.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers,

contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational product is Dexmedetomidine hydrochloride injection, US approved PRECEDEX™.

5.1. Allocation to Treatment

Within the appropriate age stratum, subjects will be randomized in a 1:1:1 ratio on Study Day 1 to the DEX low dose, middle dose or high dose group. Allocation of subjects to dose groups will proceed through the use of an interactive response technology (IRT) system (interactive Web-based response [IWR]).

Once the signed informed consent has been provided by the parent/legal guardian and assent (as required by the Institutional Review Board [IRB]/Independent Ethics Committee [IEC]) has been provided by the subject, the blinded site staff will screen the subject in the IRT system and obtain a single subject identification number (SSID) which will be used to identify the subject throughout the study. Subjects will be numbered sequentially. The subject must keep that number throughout the study even if he or she transfers to another site. A subject who discontinues or is withdrawn from the study prior to randomization and who re-screens at a later time must be assigned a new subject number. A subject number must never be reassigned or reused for any reason. The investigator must maintain a log linking the subject number to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality. Information that could identify a subject will be masked on material received by the sponsor.

To randomize an eligible subject, the blinded personnel will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, the subject number, subject date of birth and the subject's weight. The

blinded personnel will only be provided with a randomization number which must be recorded on the case report form (CRF). The IRT system will provide them a confirmation report containing the above information, which must be retained in the blinded site file.

The designated unblinded dispenser(s) will receive notification that a subject has been randomized into the study and will be provided with the subject number, weight, date of birth with age, randomization number, dose group assignment, loading dose per kg in mcg/kg, total loading dose in mcg, total loading dose in mLs, loading dose concentration in mcg/mL, loading dose IV rate in mL/hr to be given over 10 minutes, maintenance dose per kg in mcg/kg/hr, maintenance dose in mcg/hr, maintenance dose concentration in mcg/mL, maintenance dose IV rate in mL/hr (ie, all values used in determining the infusion rates), number of vials needed and the dispensable unit(s) (DU) or container number(s) to be used. Once subject numbers, randomization numbers and DU or container number(s) have been assigned, they cannot be reassigned. This notification must be retained by the unblinded dispenser in the unblinded site files.

A study specific IRT manual will be provided that will include IRT contact information and details on the use of the IRT system for this study.

A study specific IP manual will provide dosing and administration instructions and investigational product dilution instructions for this study.

All manuals will be provided separately.

5.2. Breaking the Blind

The investigational product dose is blinded to the sponsor, investigator and subject.

At the initiation of the study, the investigator site will be instructed on the method for breaking the blind. The method will be an electronic process. Sites must not contact the unblinded dispenser for this information. Blinding codes should be broken only in exceptional circumstances when knowledge of the actual treatment code is absolutely essential for further management of the subject. Investigators are encouraged to discuss with a member of the study team if they believe that breaking the blind is necessary. When the blinding code is broken, the reason must be fully documented in the source documents and entered on the CRF.

5.3. Subject Compliance

The investigational product will be administered as a single loading dose infusion followed by a maintenance dose infusion by the appropriately designated study staff at the investigator site. Subjects will not be assessed for dosing compliance.

5.4. Investigational Product Supplies

5.4.1. Dosage Form(s) and Packaging

Precedex™ (dexmedetomidine hydrochloride) Injection, Concentrate, will be provided by Pfizer Inc. as vials for IV infusion following dilution of the concentrate. Precedex Injection,

Concentrate, 200 mcg/2 mL (100 mcg/mL) vials will be supplied in a 2 mL clear glass flip-top vial and sealed with a coated stopper and an aluminum overseal with an aqua flip-off cap. Each vial will be packaged in an individual carton and labeled according to local regulatory requirements.

Each carton will contain a single vial of study medication, and each carton will be identified with a unique DU or container number. Each carton will be packaged with a tamper-resistant seal. The sponsor must be notified of any investigational product in which the tamper-resistant seal has been broken and this medication should not be used. Further details will be detailed in the Investigational Product Manual (IP Manual). The IP is presented as a sterile, clear, colorless concentrate solution for IV administration. Each vial contains 200 mcg of Dexmedetomidine in 2 mL of 0.9% sodium chloride solution. Each mL contains 100 mcg of dexmedetomidine and 9000 mcg of sodium chloride in water and must be diluted before use. The solution is preservative-free and contains no additives or chemical stabilizers. Each vial is for single-use only.

The intended dose will be diluted to a concentration not to exceed 4 mcg/mL. Each vial must be diluted as described in the IP Manual to achieve the appropriate concentration for each subject's treatment group assignment prior to administration. Specific instructions for dilution will be provided separately in the IP Manual.

5.4.2. Preparation and Dispensing

The unblinded dispenser will prepare the investigational product from the carton(s) with the unique DU or container number(s) assigned by the IRT. The IP will be dispensed on Day 1 by the unblinded dispenser to the blinded study staff who will administer the blinded loading and maintenance doses to the subject.

The site should be instructed to maintain the product in the cartons provided, and the cartons should not be opened until the investigational product is to be diluted for administration.

The number of vials dispensed will be sufficient for preparing the subject's dose based on the randomization to the low, middle, or high dose level. See the IP Manual for instructions on how to prepare the IP for administration. The IP preparation and dispensation is the responsibility of and requires oversight by an appropriately qualified and experienced unblinded site pharmacist as allowed by local, state, and institutional guidance who must sign the Preparation Records. For this study, third-party blind will be used to ensure the integrity of the blind. The IP dose will be administered blinded to the subject by site staff. The blinded study medication must be administered by a site physician experienced in delivering sedation and either the PI, or a sub-investigator (subI) who meets the criteria for PI and is listed on the 1572, must be present. The sponsor, subject and investigator will be blinded to the dose of DEX.

5.5. Investigational Product Administration

Subjects enrolled into the study will be randomized to receive one of three DEX dosing regimens (Low, Middle, or High), each consisting of an IV loading dose that is immediately

followed by an IV maintenance infusion that will continue for the duration of the MRI scan. DEX must be administered through a peripheral IV line that is not a subclavian line, peripherally inserted (or percutaneous indwelling) central catheter (PICC) line or other type of central catheter.

The loading and maintenance infusion doses will be given at the stable, pre-defined doses as described below and may not be modified, but the infusion may be discontinued if clinically indicated. The loading dose will be administered over 10 minutes:

Blinded dose levels for subjects ≥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

Blinded dose levels for subjects ≥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

Refer to the IP Manual for instructions on how to administer the investigational product. Investigational product administration details including start time, stop time and IV rate in mL/hour will be recorded on the CRF.

5.6. Rescue Propofol Medication

Once the DEX loading dose has been administered and the maintenance dose started, if an adequate level of sedation is not achieved within 5 minutes after the start of the DEX maintenance infusion, concomitant PRO may be given per clinical judgment to ensure that an adequate sedation level is achieved to start the scan. The target sedation level is 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.").[27]

Concomitant PRO should be administered as needed through completion of the scan to maintain adequate subject sedation per PI clinical judgment. If it is needed, PRO should 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 be given as needed for subject movement/wakening. Following each additional PRO bolus, there must be 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 be made in 25 or 50 mcg/kg/min increments without a corresponding PRO bolus. The PRO maintenance infusion may also be decreased in 25 or 50

mcg/kg/min increments as needed to maintain adequate subject sedation, or it may be discontinued if clinically indicated.

PRO administration details including start time, stop time, bolus doses in mg/kg and maintenance dose rates in mcg/kg/min will be recorded on the CRF.

PRO will be supplied by each individual study site.

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

5.7. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products including PRO are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

See the IP manual for storage conditions of the product.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

5.8. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

5.8.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). All used and unused supplies must be inventoried and accounted for by the study monitor. When notified by the Sponsor that it is appropriate, all used, partially used, or unused vials may be destroyed according to site-specific standard operating procedure (SOP) for clinical supply destruction after accountability has been completed by the study monitor. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.9. Prior Treatments

The start and stop dates of administration for all medications and non-pharmacologic therapies received by the subject for the 4-week period before randomization will be recorded on the subject's CRF.

5.10. Concomitant Treatments

All medications and non-pharmacologic therapies that the subject receives from randomization through the Day 29 Long-term Follow-up Visit will be recorded on the appropriate CRF along with the dates of administration and dosages. Time will also be collected for concomitant treatments with a start date on Day 1. Any questions about whether use of a concomitant medication or treatment is prohibited or permitted during a subject's study participation should be discussed with the Pfizer medical representative.

5.10.1. Required Treatments

The following treatments are concomitant treatments or procedures that are ***required*** during the DEX administration.

Subjects will be administered supplemental IV fluids during the DEX infusion that will be administered at a minimum maintenance rate in mL/hr per the following formula:

- 4 mL/kg/hr for the first 10 kg of weight; and
- 2 mL/kg/hr for the next 10 kg of weight; and
- 1 mL/kg/hr for every additional 1 kg of weight.

However, sites may limit the IV rate to a maximum of 100 mL/hr for subjects weighing ≥60 kg if appropriate per PI judgment/local practice. Please refer to the IP Manual for the list of permitted IV fluids that may be used. The use, type and rate of maintenance fluid administration following discontinuation of the DEX infusion will be at site discretion.

5.10.2. Permitted Concomitant Treatments

The following treatments are concomitant treatments or procedures that are ***permitted*** throughout study participation.

- Supplemental oxygen (O_2) is permitted, but if used as prophylaxis, it should be administered via nasal cannula at a rate of 1-3 L/min or via face mask at a rate of at least 6 L/min and must not interfere with $EtCO_2$ concentration monitoring throughout the MRI scan. Oxygen may also be administered as interventional treatment if needed. See Section 8.4.1.3.
- Contrast solution is permitted but must be administered while the DEX and/or PRO infusion is paused. Site-specific standard procedures for contrast solution infusion should be followed.
- If the Investigator believes that placement of IV access could provoke anxiety or added discomfort to the subject, they may utilize one of the following options below in an effort to allay subject anxiety:
  - Topical or local anesthetic;
  - Gas induction that is administered via mask with either sevoflurane-oxygen, sevoflurane-nitrous oxide-oxygen mixtures or nitrous oxide-oxygen. As soon as the patient becomes compliant, intravenous cannulation should occur. Following intravenous cannulation, the inhalation agents should be turned off and the patient should be administered 100% oxygen. To wash out these agents as fast as possible, a high fresh gas flow of 100% oxygen should be administered. The Fractional Inspiratory Oxygen (FIO_2), Fractional Inspiratory (FI), End Tidal (ET) sevoflurane/nitrous oxide should be monitored during this induction process. When the ET sevoflurane/nitrous oxide is below 0.1% and the subject is awake and not agitated the infusion of the DEX loading dose may commence.

5.10.3. Prohibited Concomitant Treatments

The following treatments are concomitant treatments or procedures that are ***prohibited*** from randomization through the Day 2 Follow-up Visit (24-Hour Post-Treatment Period) or as otherwise specified below. Subjects requiring a prohibited treatment, procedure or medication to control a medical condition should ***not*** be enrolled.

- Drugs administered during the study drug infusion that may affect the sedation assessment such as anesthetics (other than topical/local), sedatives, hypnotics and opioids other than DEX or PRO.

- Prophylactic use of atropine or other medications to prevent bradycardia are prohibited, but they may be used as interventional treatment if needed. See Section 8.4.1.3.
- Current or recent use of digoxin within the past month.
- Subjects receiving anti-depressants (eg, fluoxetine) for chronic therapy prior to enrollment in the study may be enrolled and continue the use of the prior antidepressant(s); however, these agents are not to be introduced during the 48-hour period prior to study drug infusion through the Day 2 Follow-up Visit (24-Hour Post-Treatment Period).
- Any neuromuscular blocking agents.
- Any drugs contraindicated with the use of DEX or PRO.
- Alpha-2 agonists/antagonists other than DEX within 14 days prior to study drug start or during study drug infusion. (eg, clonidine, guanfacine, etc).
- Agents to induce sleep (eg, triazolam, diphenhydramine, etc) during the study drug infusion other than those listed in Section 5.10.2 Permitted Concomitant Treatments.
- Insulin administered for Type I or Type II DM.
- Planned medical procedure during the MRI scan or post-MRI recovery period. Non-interventional/observational procedures are not exclusionary.

6. STUDY PROCEDURES

6.1. Screening

All subjects must complete the procedures listed below during a Screening Visit on or up to 3 days before Day 1.

The study will be thoroughly explained to the subject and the subject's legal guardian(s) as appropriate. The investigator must ensure that each trial subject, or his/her legal guardian(s), is fully informed about the nature and objectives of the trial and possible risks associated with participation. If the subject wishes to participate in the study and the legal guardian(s) desires the subject to participate in the study, an IRB/IEC-approved informed consent form will be signed and dated by the subject or legal guardian(s) as appropriate, before any procedures are performed that are specific to this study. The informed consent form must be agreed to by Pfizer and the IRB/IEC and must be in compliance with ICH Good Clinical Practice (GCP), local regulatory requirements, and legal requirements.

The signed documents will be retained at the site and the investigator or person designated by the investigator must document in the source documents that informed consent was obtained.

Each subject will be assigned a unique subject number via the IRT system. The Day 1 Visit is the date of the MRI scan.

The following information/assessments will be collected.

1. Informed consent/assent. Signed informed consent/assent must be obtained prior to conducting any tests, assessments or procedures.
2. Subject Number assignment via IRT.
3. Subject demography: date of birth, sex, race, and ethnicity.
4. Presence of chronic conditions and general medical history of relevance including surgical procedures. Start and stop dates should be included if known.
5. Eligibility assessment.
6. Physical examination including the following body systems: general appearance, head, ears, eyes, nose, mouth, throat, neck, lungs, heart, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological. The physical examination (PE) will be conducted by a physician, trained physician's assistant or nurse practitioner as acceptable according to local regulation.
7. Contraception check. The investigator must assess and document in the source if the subject is biologically capable of having/fathering children and if the subject continues to be or has become sexually active. If yes, their method of contraception and confirmation of its consistent and correct use must also be documented in the source documents.
8. Vital signs measurements, including height (or length as appropriate), weight, temperature, heart rate, respiratory rate, SpO_2 and blood pressure including MAP. Vital signs measurements should be taken in a supine position as much as possible.
9. Two-minute rhythm strip and/or 12-lead ECG as required. A 12-lead ECG will be performed if clinically significant abnormalities are noted on the rhythm strip. If a site does not have the capability to obtain a hard copy rhythm strip, the 12-lead ECG may be performed in lieu of the rhythm strip. Subjects with a known history of cardiac disease will be required to have a 12-lead ECG performed. Rhythm strips and 12-lead ECGs must be evaluated for abnormalities by a physician experienced in pediatric rhythm interpretation and hard copies retained. The investigator is responsible for reviewing, signing and dating the interpretations. If a clinically significant observation is noted, please contact the Pfizer Medical Representative prior to randomization.
10. Adverse events (AEs)/serious adverse events (SAEs) will be collected from the time the informed consent is obtained.
11. Collection of prior treatment information.

The presence of all required inclusion criteria and the absence of all exclusion criteria must be recorded in the source documents. Subjects meeting all of the inclusion criteria and none of the exclusion criteria will be eligible to randomize in the study.

6.1.1. Screen Fail Subject

A subject who does not meet one or more inclusion criteria or meets one or more exclusion criteria will be considered a screen failure and they should not be randomized.

Screen failure subjects may re-screen at a later date. If a subject chooses to re-screen, a second informed consent must be obtained and documented, a new subject number must be assigned, and **all** screening tests and procedures must be repeated. All results must be obtained and reviewed before the subject may be randomized. Subjects needing to be re-screened more than once must first be discussed with the Pfizer Medical Representative.

6.2. Day 1 Period 1 (MRI scan)

All tests and procedures described in Section 6.1 and those prior to randomization listed below must be completed and all results reviewed before the subject may be evaluated for eligibility to randomize. Subjects who meet all inclusion criteria and do not meet any exclusion criteria will be randomly assigned by age to one of three dose groups. The following will be completed before randomization:

1. Eligibility assessment.
2. Temperature and weight. If Screening and Day 1 occur on the same day, the temperature and weight do not need to be repeated before randomization.
3. Laboratory evaluation: Urine dipstick or whole-blood qualitative hCG pregnancy test that can be performed at the bedside for all female subjects of child-bearing potential. Serum qualitative or quantitative hCG pregnancy tests are not permitted.

The following will be completed after randomization:

1. Vital signs measurements, including heart rate, respiratory rate, SpO_2 and blood pressure including MAP should be obtained with the subject in a supine position as much as possible. Heart rate, respiratory rate, SpO_2, blood pressure and MAP will be measured within approximately 5 minutes before the loading dose to obtain Baseline values and those values will be documented on the CRF. Heart rate, respiratory rate, SpO_2, blood pressure and MAP will be measured every 5 (±1) minutes once the loading dose has started until the end of the MRI scan and the values documented on the CRF. Heart rate, respiratory rate and SpO_2, as well as blood pressure where available, will also be monitored between scheduled readings either per site equipment monitoring standards or more frequently as deemed clinically necessary from the start of the study treatment loading dose through the post-MRI recovery period. All vital sign values obtained from a monitoring equipment download need to be reviewed for adverse events regardless of their collection frequency. If any vital sign values between the required scheduled readings meet the criteria for a protocol-specified adverse event, the AE needs to be reported. Nadir values for HR, RR and SpO_2 vital sign measurements during the course of the sedation will also be obtained from the telemetry monitor data and documented on the CRFs. Nadir values for systolic BP and MAP during the course of the sedation will be identified programmatically from the data entered on the CRF.

If heart rate decreases >20% from Baseline and is outside the normal range, a blood pressure measurement including MAP should be repeated at approximately 2-minute intervals until the heart rate returns to the normal range. If systolic blood pressure decreases ≥30% from Baseline and is outside the normal range, a blood pressure measurement including MAP should be checked approximately 1 minute later. If the systolic blood pressure remains outside the normal range, measurements should be repeated at approximately 2-minute intervals until the systolic blood pressure returns to the normal range. Normal ranges are provided in Appendix 8, Normal Ranges by Age (Nelson Textbook of Pediatrics, 20th Ed, 2016). Baseline values are those obtained at Day 1 Period 1 within approximately 5 minutes before the start of the DEX loading dose.

2. $EtCO_2$ will be monitored from the start of the study treatment loading dose through the MRI scan. $EtCO_2$ data will not be collected on a CRF.

3. Continuous cardiac telemetry monitoring is required beginning just prior to the start of the study treatment loading dose and continuing through the post-MRI recovery period. New or worsening clinically significant abnormalities not already defined in Section 8.4.1, Protocol-Specified Adverse Events, will also be documented as adverse events on the CRF.

4. Peripheral IV line insertion if needed. DEX must be administered through a peripheral IV line that is not a subclavian line, PICC line or other central catheter.

5. PSSS sedation ratings will be obtained prior to the study treatment loading dose, immediately following administration of the loading dose, and at 5 (±1) minute intervals throughout the duration of the study treatment infusion and MRI scan.

6. Administration of DEX. Subjects will receive a single blinded IV Loading Dose of DEX over 10 minutes followed by a blinded IV Maintenance Infusion Dose of DEX per their age and dose group assignment described in Section 5.5 Investigational Product Administration. The infusion rate of the loading and maintenance dose IV infusions in mL/hour will be provided by the third-party unblinded dispenser. The sponsor, subject and investigator will remain blinded to the dose assignment. Dose adjustments of DEX are not permitted.

7. Open-label PRO may be administered if needed per Section 5.6 Rescue Propofol Medication to achieve and maintain an adequate level of sedation in the clinical judgment of the PI. The target sedation level is indicated by a PSSS score of 2.

8. Supplemental IV fluids will be administered during the DEX infusion at a maintenance rate per Section 5.10.1. Please refer to the IP Manual for the list of permitted IV fluids that may be used.

9. The MRI scan may commence once the subject has achieved an adequate level of sedation. Any necessary contrast solution must be administered while the DEX

and/or PRO infusion is paused. Site-specific standard procedures for contrast solution infusion should be followed.

10. AE/SAE monitoring.

11. Collection of concomitant treatment information.

6.3. Day 1 Period 2 (Post-MRI Recovery)

Subjects must be monitored per protocol requirements for a minimum of 1 hour; this must occur in a post-procedure recovery area such as a post-anesthesia care unit (PACU), recovery room or other hospital area where the required monitoring can be achieved. After 1 hour, subjects will meet criteria to leave this area when the subject attains a minimum Modified Aldrete Score of 9, is tolerating oral fluids and if applicable, any institution-specific discharge criteria have also been met.

1. Vital signs measurements, including temperature, heart rate, respiratory rate, SpO_2 and blood pressure including MAP should be obtained with the subject in a supine position as much as possible. Body temperature will be measured when the subject arrives in the post-procedure recovery area and when they meet the criteria to leave this area. Heart rate, respiratory rate, SpO_2, blood pressure and MAP will be measured upon arrival in the post-procedure recovery area and every 5 (±1) minutes for the first 15 minutes, and every 15 (±5) minutes until the subject meets the criteria to leave this area described above. These values will be documented on the CRF. Heart rate, respiratory rate and SpO_2, as well as blood pressure where available, will also be monitored between scheduled readings either per site equipment monitoring standards or more frequently as deemed clinically necessary from the start of the study treatment loading dose through the post-MRI recovery period. All vital sign values obtained from a monitoring equipment download need to be reviewed for adverse events regardless of their collection frequency. If any vital sign values between the required scheduled readings meet the criteria for a protocol-specified adverse event, the AE needs to be reported. If heart rate decreases >20% from Baseline and is outside the normal range, a blood pressure measurement including MAP should be repeated at approximately 2-minute intervals until the heart rate returns to the normal range. If systolic blood pressure decreases ≥30% from Baseline and is outside the normal range, a blood pressure measurement including MAP should be checked approximately 1 minute later. If the systolic blood pressure remains outside the normal range, measurements should be repeated at approximately 2-minute intervals until the systolic blood pressure returns to the normal range. Normal ranges are provided in Appendix 8, Normal Ranges by Age (Nelson Textbook of Pediatrics, 20th Ed, 2016). Baseline values are those obtained at Day 1 Period 1 within approximately 5 minutes before the start of the DEX loading dose.

2. Continuous cardiac telemetry monitoring is required beginning just prior to the start of the study treatment loading dose and continuing through the post-MRI recovery period. New or worsening clinically significant abnormalities not already defined in

Section 8.4.1, Protocol-Specified Adverse Events, will also be documented as adverse events on the CRF.

3. Modified Aldrete Score will be performed on arrival at the post-procedure recovery area and every 15 (±5) minutes until the subject is deemed suitable for discharge from that area. Every attempt should be made to collect Modified Aldrete Scores for subjects less than 1 year of age.

4. PAED score will be performed after the subject awakens following arrival at the post-procedure recovery area and every 15 (±5) minutes until the subject is deemed suitable for discharge from that area. If any total score on the PAED is 10 or greater, subjects should be evaluated for emergence delirium, treated as appropriate and the PAED assessment frequency should be increased to every 5 (±1) minutes until the PAED score is below 10 or the subject leaves that area.

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6. AE/SAE monitoring.

7. Collection of concomitant treatment information.

6.4. Follow-up

6.4.1. Day 2 Follow-up

The Day 2 Follow-up visit will be completed 24 hours (±2 hours) following discontinuation of DEX. Contact with the subject or parent/legal guardian may be done via a phone call.

1. AE/SAE monitoring (see the Time Period for Collecting AE/SAE Information Section 8.1.4).

2. Collection of concomitant treatment information.

6.4.2. Day 29 Long-term Follow-up

The Day 29 Long-term Follow-up contact will be completed at least 28 calendar days, and up to 31 calendar days after the last administration of the investigational product. Contact with the subject or parent/legal guardian will be done via a phone call.

1. AE/SAE monitoring (see the Time Period for Collecting AE/SAE Information Section 8.1.4).

2. Contraception check (see the Contraception Section 4.5.1).

3. Collection of concomitant treatment information.

6.5. Subject Withdrawal / Early Termination

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal / Early Termination section)) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

Subjects who do not complete the MRI scan will be considered discontinued subjects. Subjects who have a medical procedure performed during the MRI scan must be discontinued. The Day 1 Period 1 assessments described in Section 6.2 and the Day 1 Period 2 assessments described in Section 6.3 should be completed as appropriate. The Follow-up Visits should be completed whenever possible.

Withdrawal of consent:

Subjects/parents/legal guardians who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject/parent/legal guardian specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects/parents/legal guardians should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post-treatment study follow-up and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject/parent/legal guardian after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the subject to 1 registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. Study sites should document 3 attempts to contact subjects and/or parent(s)/legal guardian(s) as appropriate. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. The final attempt should be a certified letter or use of a courier to the subject and/or parent(s)/legal guardian(s) to attempt contact. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, and request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.
Subjects who withdraw from the study will not be replaced.

6.5.1. Adverse Events Requiring Subject Withdrawal from Treatment

The following adverse events should be assessed as described below to determine if the event requires discontinuation of treatment. Refer to Section 8.4.1.1 for definitions of bradycardia, hypotension, hypertension and paradoxical agitation reaction. Subjects experiencing an AE that requires a medical procedure be performed during the MRI scan must be discontinued.

- **Bradycardia** that is not responsive to standard treatment (including glycopyrrolate or atropine). The DEX infusion will be discontinued and the subject treated as clinically indicated. This adverse event should be reported as an SAE.

- **Hypotension** that is not responsive to standard treatment (including fluid resuscitation and vasopressor/inotropic support). The DEX infusion will be discontinued and the subject treated as clinically indicated. This adverse event should be reported as an SAE.

- **Hypertension** that is not responsive to standard treatment. The DEX infusion will be discontinued and the subject treated as clinically indicated. This adverse event should be reported as an SAE.

- **Paradoxical agitation reaction** occurring during the study drug infusion period. The DEX infusion will be discontinued and the subject treated as clinically indicated. This adverse event should be reported as an SAE.

- **Adverse event requiring intubation or LMA (laryngeal mask airway)**. The DEX infusion will be discontinued and the subject treated as clinically indicated. This adverse event should be reported as an SAE.

- **Second- or third-degree heart block**. The DEX infusion will be discontinued and the subject treated as clinically indicated. Second-degree block adverse events should

be reported as an SAE if appropriate. All third-degree block adverse events should be reported as an SAE.

6.5.2. Adverse Events Requiring Assessment for Subject Withdrawal from Treatment

The following adverse events should be assessed as described below for the Investigator to determine if the event warrants discontinuation of treatment:

- **Decreased respiratory rate** in a subject unresponsive to commands. The Investigator should determine if the DEX infusion should be discontinued and if further intervention is needed.

- **Other cardiac events** should be assessed and the Investigator should determine if the DEX infusion should be discontinued and if further intervention is needed.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

1. **AE/SAE Reporting**: adverse events and serious adverse events will be collected from the time the informed consent and assent (as appropriate) is obtained through the Day 29 Long-term Follow-up visit or final visit prior to the Day 29 Long-term Follow-up visit as appropriate and will be recorded on the CRF and source documents. There are 2 Adverse Event CRF pages used in this study: the Adverse Event Report CRF page and the Medication Error Record CRF page. See Section 8 for further information regarding adverse event reporting.

3. **Concomitant treatment recording**: concomitant medications and non-pharmacologic therapies will be collected from randomization through the Day 29 Long-term Follow-up Visit and will be recorded on the CRF and source documents.

4. **Contraception Check**: The investigator must assess and document in the source if the subject is biologically capable of having/fathering children and if the subject continues to be or has become sexually active. If yes, their method of contraception and confirmation of its consistent and correct use must also be documented in the source documents.

5. **$EtCO_2$**: end tidal carbon dioxide to be monitored through nasal cannula capnography.

6. **IV line access**: peripheral IV access is required for the study drug infusion. DEX must be administered through a peripheral IV line that is not a subclavian line, PICC line or other central catheter. Existing IV catheters being used for another purpose (eg, administration of fluids, IV antibiotics etc.) must be used with the Sponsor provided Y-connector and 3-port connector. Existing IV tubing must not be used. Topical or local anesthetics may be used as needed for IV placement.

7. **Laboratory whole-blood qualitative hCG pregnancy test**: a whole-blood test may be performed if it can be done at the bedside. Serum qualitative or quantitative hCG pregnancy tests are not permitted. The test must be conducted on Day 1 and a negative pregnancy result is required before the subject may be randomized prior to the MRI scan. Sites are expected to provide their own supplies. Subjects with an indeterminate or positive test result may not randomize in the study.

8. **Laboratory urine qualitative hCG pregnancy test: dipstick** test kits will be provided by each individual site and only kits that have a sensitivity of at least 25 milli-international units per milliliter (mIU/mL) will be approved for use in this study. A negative pregnancy result is required before the subject may be randomized. Subjects with an indeterminate or positive test result may not randomize in the study.

9. **Modified Aldrete Score**: 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. Information on qualification, training and approval to rate this scale will be provided separately. Refer to Appendix 4.

10. **PAED (Pediatric Anesthesia Emergence Delirium Scale)**: A validated 5-item rating scale to measure emergence delirium (ED) in children 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 ED increases directly with the total score. Information on qualification, training and approval to rate this scale will be provided separately. Refer to Appendix 5.

11. **PE**: includes the following body systems: general appearance, head, ears, eyes, nose, mouth, throat, neck, lungs, heart, abdomen, musculoskeletal, extremities, skin, lymph nodes, neurological. The PE will be conducted by a physician, trained physician's assistant or nurse practitioner as acceptable according to local regulation. Results must be recorded in the source documents and any significant findings documented on the appropriate CRF pages.

12. **Prior treatment recording**: prior medications and non-pharmacologic therapies will be collected for the 4-week period before randomization and will be recorded on the CRF and source documents.

13. **PSSS (Pediatric Sedation State Scale)**: 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. Information on qualification, training and approval to rate this scale will be provided separately. Refer to Appendix 6.

14. **Rhythm strip/12-lead ECG/cardiac telemetry monitoring:** The 2-minute rhythm strip and/or 12-lead ECG at Screening should be obtained and hard copies retained after the subject has been calm for at least five (5) minutes and should be obtained prior to vital signs collection. A physician experienced in pediatric rhythm interpretation will read and evaluate the tracing for abnormalities, which will be documented on the appropriate CRF. Clinically significant abnormalities on the rhythm strip suggestive of AV conduction block or sustained cardiac arrhythmia will require that a 12-lead ECG be performed. A 12-lead ECG will be required at Screening for subjects with known history of cardiac disease. If a site does not have the capability to obtain a hard copy rhythm strip, the 12-lead ECG may be performed in lieu of the rhythm strip. The investigator is responsible for reviewing, signing and dating the interpretations. Cardiac telemetry monitoring is required beginning just prior to the start of the study treatment loading dose and continuing through the post-MRI recovery period. Clinically significant abnormalities noted on cardiac telemetry will be documented as adverse events.

15. **Vital signs**: includes height (or length as appropriate), weight, temperature, heart rate, respiratory rate, SpO_2, blood pressure including MAP. Measurements should be obtained with the subject in a supine position as much as possible.

    - Height (or Length): in inches or centimeters, recorded to one decimal place. The height (or length) should be measured with the subject not wearing shoes.

    - Weight: in pounds or kilograms, recorded to one decimal place will be obtained using an electronic scale. The weight should be measured with the subject not wearing shoes.

    - Height and weight values will be rounded to 1 decimal place (the nearest tenth) for calculations and documentation. To round a number to the **nearest tenth** (ie, 1 decimal place), look at the second number to the right of the decimal point (the hundredths place). If that hundredths number is 4 or less, remove all numbers to the right of the tenths place. If that hundredths number is 5 or greater, add 1 to the number in the **tenths** place, and then remove all the numbers to the right of the tenths place.

    - Heart rate: whenever possible, the subject should refrain from products containing nicotine or caffeine 2 hours before taking heart rate measurements and should rest at least 2 minutes before heart rate is measured. Once the loading dose is started, heart rate must be measured using the cardiac monitor.

    - Blood pressure (SBP, DBP and includes MAP): whenever possible, the subject should refrain from products containing nicotine or caffeine 2 hours before taking blood pressure measurements and should rest at least 2 minutes before blood pressure readings are taken. The Screening blood pressure may be measured using a manual aneroid or mercury sphygmomanometer or by an automated method (such as a Dinamap®) with a cuff appropriate to the subject's arm or leg girth as appropriate. Once the DEX loading dose is started, blood pressure must be measured using an MRI compatible automated method that will provide BP monitoring throughout the MRI scan. The site will need to retain documentation of machine calibration per the manufacturer's suggested calibration schedule.

    - Temperature: using oral, axillary, temporal scan or tympanic method measured in degrees Fahrenheit or Centigrade.

    - Respiratory rate: respirations per minute.

    - SpO_2: saturation of peripheral oxygen to be measured as a percentage using pulse oximetry.

7.1. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test with sensitivity of at least 25 mIU/mL, or a whole-blood pregnancy test that can be done at the bedside will be performed on Day 1 Period 1 (Pre-Randomization). Serum qualitative or quantitative hCG pregnancy tests are not permitted.

A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit approved by the sponsor in accordance with instructions provided in its package insert. Subjects who show an indeterminate or positive result on the urine test may not further progress in the study.

7.2. Rater Qualifications

For specific rating assessments, only qualified raters will be allowed to evaluate and/or rate subjects in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the Rater Assessment Manual provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not a waiver may be issued. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial Serious Adverse Event (CT SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.	All AEs/SAEs associated with exposure during pregnancy or breastfeeding. Occupational exposure is not recorded.	All (and EDP supplemental form for EDP). Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

All observed or volunteered events regardless of dose group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the

investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details On Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal / Early Termination section)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF. See Section 6.4.1 for adverse events requiring assessment for subject withdrawal.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs (“active collection period”) for each subject begins from the time the subject/parent(s)/legal guardian/legally acceptable representative provides informed consent, which is obtained before the subject’s participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product. At the Day 29 Long-term Follow-up visit (final telephone contact), the subject/parent(s)/legal guardian/legally acceptable representative will be contacted by telephone to inquire about SAEs, including hospitalizations, newly diagnosed chronic medical conditions and concomitant treatments since the previous study Visit.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.4.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions (SUSAR), will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease*;*
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the Medical Device Complaint Reporting Requirements section). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that,

directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;
- Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalization or significant prolongation of existing hospitalization;
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

8.4.1. Protocol-Specified Adverse Events

8.4.1.1. Changes in Blood Pressure and Heart Rate

The Investigator will assess changes in supine blood pressure and supine heart rate throughout the study. Blood pressure and/or heart rate measurements exceeding the specified limits as below will be recorded as adverse events, regardless of whether or not they result in discontinuation from the study or necessitate therapeutic medical intervention.

Vital sign (HR or BP) measurements exceeding the specified limits within the indicated time periods below are considered AEs:

- **Bradycardia:** A decrease in HR of ≥30% from Baseline and/or meets the criteria below. HR must be sustained for ≥2 consecutive measurements that are separated by at least 1 minute. If available HR values between the scheduled readings meet the criteria for bradycardia, the AE should be reported. A decrease in HR that requires intervention should also be reported as an AE (or SAE as appropriate) of bradycardia. Baseline values are those obtained at Day 1 Period 1 within approximately 5 minutes before the start of the DEX loading dose.

Study Criteria for AE of Bradycardia*	
Age	**HR**
≥1 month to <3 months	<107 bpm
≥3 months to <6 months	<104 bpm
≥6 months to <9 months	<98 bpm
≥9 months to <12 months	<93 bpm
≥12 months to <18 months	<88 bpm
≥18 months to <24 months	<82 bpm
≥2 years to <3 years	<76 bpm
≥3 years to <4 years	<70 bpm
≥4 years to <6 years	<65 bpm
≥6 years to <8 years	<59 bpm
≥8 years to <12 years	<52 bpm
≥12 years to <15 years	<47 bpm
≥15 years to <18 years	<43 bpm

*Based on 1st centile data from the HR table in Appendix 7, HR and RR Centile Chart Cut-offs for Children from Birth to 18 Years of Age (Fleming et al, Lancet 2011).

- **If bradycardia** is not responsive to standard treatment (including glycopyrrolate or atropine), the DEX infusion should be discontinued and the subject treated as clinically indicated. This adverse event should be reported as an SAE.

- **Hypotension:** A decrease in SBP of ≥30% from Baseline should be reported as an AE of hypotension. A decrease in SBP of ≥50% from Baseline should be reported as a severe AE. SBP values must be sustained for ≥2 consecutive measurements at least 5 (±1) minutes apart. If available SBP values between the scheduled readings meet the criteria for hypotension, the AE should be reported. A decrease in SBP that requires intervention should also be reported as an AE (or SAE as appropriate) of hypotension. Baseline values are those obtained at Day 1 Period 1 within approximately 5 minutes before the start of the DEX loading dose.

    - **If hypotension** is not responsive to standard treatment (including fluid resuscitation and vasopressor/inotropic support), the DEX infusion should be discontinued and the subject treated as clinically indicated. This adverse event should be reported as an SAE.

- **Hypertension:** The criteria for the definition of an adverse event of hypertension were based on the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents,[28] the Pediatric Vital Signs Reference Chart (pediatric advanced life support [PALS] normal blood pressure by age guidelines)[29] and the advice of clinical expert consultants.

    - For subjects ages ≥1 month to <1 year: Hypertension is defined as supine SBP ≥104 mm Hg and/or DBP ≥56 mm Hg measurements on ≥2 consecutive occasions taken at least 5 (±1) minutes apart and/or requires intervention. This event should be reported as an AE.

    - For subjects ages ≥1 year to <17 years: Hypertension is defined as supine SBP and/or DBP measurements that are ≥95th percentile for gender, age, and height (stature) on ≥2 consecutive occasions taken at least 5 (±1) minutes apart and/or requires intervention. The tables for hypertension assessment for this age group will be provided separately. This event should be reported as an AE.

    - **If hypertension** is not responsive to standard treatment, the DEX infusion will be discontinued and the subject treated as clinically indicated. This adverse event should be reported as an SAE.

8.4.1.2. Paradoxical Agitation Reactions

Throughout the Study Drug Infusion Period and extending into the 24-hour post-infusion observation period, the Investigator should monitor for the onset of paradoxical agitation reactions (eg, rage). The clinical features may vary with age of the subject, but the following should be used as a guide:

- Age ≥1 month to <8 years: Inconsolable crying and/or irritability that are otherwise unexplained by the subjects' current medical condition and are unable to be controlled with conventional interventions.

- Age ≥8 years to ≤17 years: Aggressive behavior and/or excessive emotional outbursts that are otherwise unexplained by the subjects' current medical condition and are unable to be controlled with conventional interventions. An example of this may include a subject that becomes physically violent that may expose healthcare personnel or themselves to harm.

In the event a paradoxical agitation reaction occurs during the study drug infusion period, the study drug will be discontinued and the subject treated as clinically indicated. The event should be reported as an AE and an SAE.

8.4.1.3. Changes in Respiratory Rate, $EtCO_2$ and SpO_2

The Investigator will assess changes in respiratory rate, changes in measurement of carbon dioxide (CO_2) concentration and oxygen saturation throughout the study. Respiratory rates, $EtCO_2$ and/or SpO_2 measurements below the thresholds outlined in the tables below will be recorded as adverse events, regardless of whether or not they result in discontinuation from the study or necessitate therapeutic medical intervention.

Thresholds for Respiratory Rate Adverse Events

Age	Respiratory Rate* (breaths per minute)	Adverse Event Term**
≥1 month to <3 months	<25	Bradypnea
≥3 months to <6 months	<24	
≥6 months to <9 months	<23	
≥9 months to <12 months	<22	
≥12 months to <18 months	<21	
≥18 months to <24 months	<19	
≥2 years to <3 years	<18	
≥3 years to <4 years	<17	
≥4 years to <6 years	<17	
≥6 years to <8 years	<16	
≥8 years to <12 years	<14	

Age	Respiratory Rate* (breaths per minute)	Adverse Event Term**
≥12 years to <15 years	<12	
≥15 years to <17 years	<11	

*Rate must be sustained for at least 2 consecutive measurements that are separated by at least one minute and/or requires intervention in order to meet the criteria for AE. If available RR values between the scheduled readings meet the criteria for bradypnea, the AE should be reported. Based on the 1st centile data from the RR table in Appendix 7, HR and RR Centile Chart Cut-offs for Children from Birth to 18 Years of Age (Fleming et al, Lancet 2011).
**This term should be used unless the decreased respiratory rate is part of a larger constellation of signs and symptoms documented as another adverse event.

Thresholds for EtO2 and SpO_2 Change Adverse Events

	Value	Adverse Event Term*
SpO_2	<90% for any duration	Hypoxia
Capnography	$EtCO_2 = 0$ for ≥30 seconds	Apnea

*These terms should be used unless the $EtCO_2$ and/or SpO_2 finding(s) are part of a larger constellation of signs and symptoms documented as another adverse event. In determining whether an apnea or hypoxia AE has occurred the clinician should verify the nasal capnograph or SpO2 monitor is in the right location and functioning properly.

Respiratory rate, SpO_2 and/or $EtCO_2$ measurements that do not meet or exceed these values will also be recorded as adverse events if they necessitate therapeutic medical intervention or the Investigator considers them to be adverse events. The date and time of occurrence and any treatment or intervention for all adverse events are to be recorded on the appropriate eCRF. Examples of interventions that should be recorded to bradypnea/hypoxia/apnea are airway repositioning, bag-mask intervention, deepening of sedation, fluid bolus, jaw thrust, CPAP, initiation of or increased oxygen, intubation, etc.

For a decrease in respiratory rate in a subject unresponsive to commands, the Investigator will determine if study drug should be discontinued and will treat the subject as clinically indicated. All interventions will be recorded in the appropriate section of the eCRF.

8.4.2. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.3. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to

progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a subject presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

8.4.4. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.4.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

  - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on

preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.4.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.4.4.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.5. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

8.4.5.1. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong subject, or at the wrong time, or at the wrong dosage strength.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

8.5. Medical Device Complaint Reporting Requirements

This section applies **only** to sites in Japan using propofol pre-filled syringes. Please refer to Appendix 9, Propofol Pre-filled Syringe Medical Device Reporting in Japan for details.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

The primary comparison will be the percent of subjects who do not require supplemental PRO in the high dose group vs. the low dose group in both age cohorts combined. The younger age cohort will be comprised of subjects aged ≥1 month to <2 years of age and the older age cohort will include subjects ≥2 to <17 years of age. The primary efficacy analysis population is the Full Analysis Set (FAS) defined as all randomized subjects who receive any amount of DEX, and for the primary and key secondary analyses, subjects who do not complete the MRI scan will be considered failures, ie, will be counted as receiving supplemental PRO. Assuming that the percent of subjects not requiring PRO are 15% and 60% in the low and high dose groups respectively, a sample size of 40 per dose group would provide a 99% power for a 2-sided test with alpha=0.05. The key secondary comparison is the percent of subjects who do not require supplemental PRO in each of the 2 age cohorts. Assuming that the percentage of subjects not requiring supplemental PRO in the older age cohort is 17% and 63% for the low and high dose groups respectively, and the percent of subjects not requiring PRO in the younger age cohort is 13% and 57% for the low and high dose groups respectively, and assuming that equal number of subjects will be enrolled in each age cohort, the power = 87% for the older age cohort and 86% for the younger age cohort. Within the older age cohort, it is planned to enroll approximately 4 subjects per dose

group for subjects ≥12 to <17 years of age, since it is expected that these subjects would require minimum sedation. Forty subjects will be enrolled per each dose level, and 20 subjects for each dose group for age cohorts ≥1 month to <2 years and ≥2 years to <17 years. The table below shows the planned enrollment in this study.

Sample Size

Age Group for Enrollment	Low Dose	Medium Dose	High Dose
≥1 month to <2 year	20	20	20
≥2 years to <12 years	16	16	16
≥12 years to <17 years	4	4	4

These assumptions were obtained from study DEX 10-16 and Mason et al publication in Pediatric Anesthesia 2008. In DEX 10-16 approximately 30% of subjects who had MRIs did not require rescue medication; the dose in study 10-16 is comparable to the middle dose in this study. In the Mason et al publication, approximately 80-90% of patients treated with 2-3 mcg/kg loading dose of DEX for MRI scans did not require supplemental anesthesia, therefore a conservative estimate of 65% was assumed. Additionally, in the DEX 10-16 study, 6% of subjects did not complete the MRI scan, so a failure rate of approximately 5% was incorporated into the assumptions of patients requiring supplemental PRO.

9.2. Analysis Populations

9.2.1. Safety Analysis Set

The safety analysis set consists of all randomized subjects who received any amount of DEX. Participants will be analyzed according to the intervention they received. In the event a subject receives a loading and/or maintenance dose that is different from the dose group to which they were randomized, the subject will be analyzed in the dose level group that corresponds to the lowest dose received. All safety analyses will be performed on the safety analysis set.

9.2.2. Full Analysis Set (FAS)

All randomized subjects who receive any amount of DEX will form the FAS. Participants will be analyzed according to the intervention to which they were randomized. This will be the primary population for efficacy analysis.

9.2.3. Efficacy Evaluable Population (EEP)

All randomized subjects who receive any amount of DEX and complete the MRI scan will form the EEP.

9.2.4. Per Protocol Population (PPP)

All subjects included in the FAS and have no major protocol deviations will form the PPP. The details of the major protocol violation criteria will be documented in a separate document prior to the end of the study.

9.2.5. Japanese Population Set (JPS)

All randomized Japanese subjects who receive any amount of DEX will form the JPS.

The JPS will be used for efficacy endpoints, demographic and baseline characteristic and safety endpoints. Participants will be analyzed according to the intervention to which they are randomized for efficacy and will be analyzed according to the intervention they receive for safety.

9.3. Efficacy Analysis

A randomized subject who received any amount of DEX but does not complete the MRI scan will be considered a treatment failure for the primary and key secondary endpoint analyses; ie, they will be counted as receiving PRO.

9.3.1. Analysis of the Primary Endpoint

The DEX high vs low dose group will be compared by Mantel-Haenszel test, and by calculating the odds ratio and 95% confidence intervals on the percent of subjects not requiring supplemental PRO. All age cohorts will be combined. The primary analysis will be performed based on the FAS. The same analysis will be repeated on the EEP and PPP.

9.3.2. Analysis of the Key Secondary Endpoint

The method of analysis for the primary endpoint will be repeated for the key secondary endpoint for each age cohort based on the FAS. The same analysis will be repeated on the EEP and PPP.

9.3.3. Analysis of Other Secondary Endpoints

The method of analysis for the primary endpoint will be repeated for the secondary endpoints comparing the low dose to the medium dose and the medium dose to the high dose, overall and within each age cohort based on the FAS, EEP and PPP.

The total amount and the weight and time adjusted amount (per kg per minute) of PRO use will be summarized for each dose group with descriptive statistics (N, mean, standard deviation [SD], median, minimum, Q1, Q3, and maximum). The weight- and time-adjusted difference between treatment groups (high dose and low dose, and medium dose and low dose and high dose versus medium dose) will be assessed using two-way analysis of variance (ANOVA) when assumption of normal distribution is reasonable or by nonparametric tests when this assumption is not met.

Emergence time (defined as the time from the end of the MRI scan to when the subject meets a Modified Aldrete Score ≥9) will be summarized and compared between dose groups using

Kaplan Meier methodology. Subjects who are withdrawn or discharged from the recovery area without reaching an Aldrete score ≥9, will be considered as having censored time computed from the end of the MRI scan to the time of the last vital signs assessment. Zero minute will be used as the censored time if no vital signs are taken during the post-MRI recovery period.

Additionally, the difference between dose levels in percent of time at the target sedation rating scale score (PSSS rating of 2) following the administration of the DEX loading dose and during the DEX maintenance infusion will be assessed using the Wilcoxon test.

Time (in minutes) from the onset of the DEX infusion to the first dose of PRO will be summarized using the Kaplan-Meier method. Subjects that do not receive any additional PRO will be considered as having a censored time. The censored time to the first dose of PRO for additional sedation will be computed as the length of time from the onset of the DEX infusion up to the time the DEX infusion is stopped.

Efficacy analyses will be conducted for all age cohorts combined and by each age cohort.

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9.5. Safety Analysis

All safety analyses will be performed on the safety analysis set.

Descriptive statistics (quantitative variables: arithmetic mean, SD, median, minimum, and maximum, categorical and ordinal variables: proportion of subjects) will be calculated for quantitative safety data as well as for the change from baseline, when appropriate. Data analyses will be presented by dose level, overall and within each age cohort. Baseline values are those obtained at Day 1 Period 1 within approximately 5 minutes before the start of the DEX loading dose.

TEAEs will be analyzed by dose level, overall, and for each age cohort according to the Medical Dictionary for Regulatory Activities system organ class and preferred term. Additionally, the proportion of subjects with protocol-specified adverse events of bradypnea, hypoxia, apnea, hypotension, hypertension, bradycardia and paradoxical agitation reaction and the proportion of subjects with such events requiring intervention will be summarized for each age cohort and each dose level. Pre-specified criteria will be used to identify the protocol-defined adverse events mentioned above.

The proportion of subjects who completed the MRI scan and required artificial ventilation or intervention to restore baseline or normal hemodynamic status will also be summarized. The incidence of individual adverse events during MRI sedation will be descriptively summarized for each dose level, including the total adverse events.

The types of individual interventions and the total number of interventions will be descriptively summarized at each dose level and for each age cohort (ie, airway repositioning, bag-mask intervention, deepening of sedation, fluid bolus, jaw thrust, CPAP, initiation of or increased oxygen, intubation, etc).

Vital sign measurements and hemodynamic and respiratory parameters will be summarized descriptively by dose level and age cohort.

Prior and concomitant medications will be summarized according to WHODRUG Dictionary. The number and percentage of subjects who used prior medications (by preferred term) will be tabulated by dose level and age cohort. The number and percentage of subjects who used concomitant medications will be similarly tabulated.

DEX withdrawal symptoms, such as agitation/anxiety, rebound tachycardia and rebound hypertension will be summarized by each dose level and age cohort. A descriptive summary will be performed for the incidence of DEX withdrawal-related AEs after discontinuation of the DEX infusion.

Descriptive analyses will be performed for the PAED total score for dose level and by age cohort.

9.6. Interim Analysis

No formal interim analysis will be conducted for this study.

9.7. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC).

The E-DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the charter.

The E-DMC will be comprised of a group of experts external to Pfizer who will review accumulated safety data from this study on an ongoing basis. The E-DMC may at any time, request additional information from the Sponsor including any information they feel is relevant. Based on these reviews, the E-DMC will have the capacity to make recommendations to Pfizer that might impact the future conduct of the trial. These may include amending safety-monitoring procedures, modifying the protocol or consent/assent, terminating the study, or continuing the study as designed.

The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include

summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

The Pfizer study team and site personnel involved in the conduct of the study will remain blinded to any unblinded study data communicated to the E-DMC.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the

IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single specific numerical code based on a numbering system defined by Pfizer. *All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code.* The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

The informed consent/assent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the subject's personal data. The investigator further must ensure that each study subject,[or his or her legally acceptable representative, or parent(s) or legal guardian if a minor,] is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative, parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

Precedex is commercially available, however it is not approved for use in pediatrics.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

End of trial in all participating countries is defined as last subject last visit (LSLV).

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of investigational product at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the PI of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

1. Petroz GC, Sikich N, James M, van Dyk H, Shafer SL, et al. A phase I, two-center study of the pharmacokinetics and pharmacodynamics of dexmedetomidine in children. *Anesthesiology.* 12 2006; 105:1098–1110.

2. Potts AL, Anderson BJ, Holford NH, Vu TC, Warman GR. Dexmedetomidine hemodynamics in children after cardiac surgery. *Pediatr Anesth.* 2010; 20:425–33.

3. Mason KP, Lerman J. Dexmedetomidine in Children: Current Knowledge and Future Applications. *Anesth & Analg.* 2011 Nov; 113:1129-1142.

4. Mason KP, Zurakowski D, Zgleszewski S, Prescilla R, Fontaine PJ, Dinardo JA. Incidence and predictors of hypertension during high-dose dexmedetomidine sedation for pediatric MRI. *Pediatr Anesth.* 2010; 20:516–523.

5. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Critical Care.* 2000 Jul; 4:302-308.

6. Sandler AN. The role of clonidine and alpha$_2$-agonists for postoperative analgesia. *Can J Anaesth.* 1996 Dec; 43(12):1191-1194.

7. Kamibayashi T, Maze M. Clinical uses of alpha^2-adrenergic agonists. *Anesthesiology.* 2000 Nov; 93(5):1345-1349.

8. Ebert TJ, Hall JE, Barney JA, et al. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology.* 2000 Aug; 93(2):382-394.

9. Jooste EH, Hammer GB, Reyes CR, Katkade V, Szmuk P. Phase IV, Open-Label, Safety Study Evaluating the Use of Dexmedetomidine in Pediatric Patients Undergoing Procedure-Type Sedation. *Front Pharmacol.* 2017; 8:529.

10. Sulton C, McCracken C, Simon HK, et al. Pediatric Procedural Sedation Using Dexmedetomidine: A Report from the Pediatric Sedation Research Consortium. *Hospital Pediatrics*. 2016; 6(9):536-44.

11. Siddappa R, Riggins J, Kariyanna S, et al. High-dose dexmedetomidine sedation for pediatric MRI. *Pediatr Anesth*. 2011; 21(2):153-158.

12. Schulte-Uentrop L, Goepfert MS. Anaesthesia or sedation for MRI in children. *Current Opinion in Anaesthesiolog*y. 2010; 23(4):513-517.

13. Vilo S, Rautianinen P, Kaisti K et al. Pharmacokinetics of intravenous dexmedetomidine in children under 11 yr of age. *Br J Anaesth*. 2008; 100(5):697-700.

14. Farag E, Argalious M, Abd-Elsayed A, et al. The use of dexmedetomidine in anesthesia and intensive care: a review. Current Pharmaceutical Design. 2012;18(38):6257-65.

15. Mason KP, Zurakowski D, Zgleszewski SE, et al. High dose dexmedetomidine as the sole sedative for pediatric MRI. *Pediatr Anesth*. 2008; 18(5):403-411.

16. Pestieau SR, Quezado ZMN, Johnson YJ, et al. High-dose dexmedetomidine increases the opioid-free interval and decreases opioid requirement after tonsillectomy in children. *Can J Anesth*. 2011; 58(6):540-550.

17. Tirotta CF, Nguyen T, Fishberger S, et al. Dexmedetomidine use in patients undergoing electrophysiological study for supraventricular tachyarrhythmias. *Pediatr Anesth*. 2017; 27(1):45-51.

18. Degos V, Le charpentier T, Chhor V, et al. Neuroprotective effects of dexmedetomidine against glutamate agonist-induced neuronal cell death are related to increased astrocyte brain-derived neurotrophic factor expression. *Anesthesiology*. 2013; 118(5):1123-1132.

19. Janke EL, Samra S. Dexmedetomidine and neuroprotection. *Seminars in Anesthesia, Perioperative Medicine and Pain*. 2006; 25(2):71-76.

20. Berkenbosch JW, Wankum PC, Tobias JD. Prospective evaluation of dexmedetomidine for noninvasive procedural sedation in children. *Pediatr Crit Care Med*. 2005; 6(4):435-439.

21. Välitalo, PA, Ahtola-Sätilä T, Wighton A, et al. Population pharmacokinetics of dexmedetomidine in critically ill patients. *Clin Drug Investig*. 2013; 33(8):579-587.

22. Potts, AL, Anderson BJ, Warman GR, et al. Dexmedetomidine pharmacokinetics in pediatric intensive care - a pooled analysis. *Pediatr Anesth*. 2009; 19(11):1119-1129.

23. Koroglu A, Teksan H, Sagr O, et al. A comparison of the sedative, hemodynamic, and respiratory effects of dexmedetomidine and propofol in children undergoing magnetic resonance imaging. *Anesth & Analg*. 2006; 103(1): 63-67.

24. Boriosi JP, Eickhoff JC, Klein KB, Hollman GA. A retrospective comparison of propofol alone to propofol in combination with dexmedetomidine for pediatric 3T MRI sedation. *Pediatr Anesth*. 2017; 27(1):52-59.

25. Precedex™ [Package Insert]. Hospira Inc., Lake Forest, IL; May 2016.

26. Constantin JM, Momon A, Mantz J, Payen JF, De Jonghe B, Perbet S, et al. Efficacy and safety of sedation with dexmedetomidine in critical care patients: a meta-analysis of randomized controlled trials. *Anaesth Crit Care & Pain Med*. 2016; 35(1):7–15.

27. Cravero JP, Askins N, Sriswasdi P, et al. Validation of the Pediatric Sedation State Scale. *Pediatrics.* 2017; 139(5): e20162897.

28. 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: 555-578.

29. Pediatric Vital Signs Reference Chart. http://www.pedscases.com/pediatric-vital-signs-reference-chart; April 2016.

Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ASA	American Society of Anesthesiologists
AST	aspartate aminotransferase
AV	atrioventricular
BP	blood pressure
BPM	beats per minute
CHOP	Children's Hospital of Philadelphia
CK	creatine kinase
CNS	Central nervous system
CO_2	carbon dioxide
COVID-19	coronavirus disease 2019
CPAP	continuous positive airway pressure
CRF	case report form
CRL	complete response letter
CSA	clinical study agreement
CT	computed tomography
CT SAE	clinical trial serious adverse event
DBP	diastolic blood pressure
DEX	dexmedetomidine
DILI	drug-induced liver injury
DM	diabetes mellitus
DMC	data monitoring committee
DU	dispensable unit(s)
EC	ethics committee
ECG	electrocardiogram
ED	emergence delirium
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EEG	electroencephalogram
EEP	Efficacy evaluable population
ET	End tidal
$EtCO_2$	end-tidal carbon dioxide
EU	European Union
EudraCT	European Clinical Trials Database
FAS	Full analysis set
FI	Fractional Inspiratory
FIO_2	Fractional Inspiratory Oxygen

Abbreviation	Term
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
hCG	Human chorionic gonadotropin
HR	heart rate
HTN	hypertension
ICH	International Conference on Harmonisation
IB	Investigator brochure
ICU	intensive care unit
ID	identification
IEC	Independent Ethics Committee
IM	intramuscular
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IV	intravenous
IWR	interactive web response
J-PI	Japan Package Insert
JPS	Japan population set
KG	kilogram
LFT	liver function test
LMA	laryngeal mask airway
LSLV	last subject last visit
MAP	mean arterial pressure
MCG	microgram
mIU/mL	milli international units per milliliter
mL	milliliter
MM HG	millimeters of mercury
MRI	magnetic resonance imaging
N/A	not applicable
NI-MDS	non-intubated, spontaneous breathing, moderate to deep sedation
N-PASS	Neonatal Pain, Agitation and Sedation Scale
O_2	oxygen
PACU	post-anesthesia care unit
PAED	Pediatric Anesthesia Emergence Delirium Scale
PCD	primary completion date
PD	Pharmacodynamics(s)
PE	physical examination
PI	principal investigator
PICC	peripherally inserted (or percutaneous indwelling) central catheter

Abbreviation	Term
PICU	pediatric intensive care unit
PK	pharmacokinetic
PO	per orum (oral)
PPP	Per protocol population
PPS	pediatric procedural sedation
PT	prothrombin time
PREA	Pediatric Research Equity Act
PRO	propofol
PSSS	Pediatric Sedation State Scale
PWR	Pediatric Written Request
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOP	standard operating procedure
SpO_2	saturation of peripheral oxygen
SRSD	single reference safety document
SubI	sub-investigator
SUSAR	suspected unexpected serious adverse reaction
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TTE	transthoracic echocardiogram
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
UMSS	University of Michigan Sedation Scale
US	United States
U/S	ultrasound
USPI	United States Package Insert
Vd	volume of distribution
Vd_{ss}	Steady-state volume of distribution

Appendix 2. Simulated Pharmacokinetic Profiles of Dexmedetomidine in Pediatric Subjects Undergoing Procedural Sedation

Background

The pharmacokinetics (PK) of dexmedetomidine (DEX) has been well characterized in adult intensive care unit (ICU) patients. In adults, following intravenous (IV) administration, DEX exhibits a rapid distribution phase with a distribution half-life (t½) of approximately 6 minutes; a terminal elimination $t_{½}$ of approximately 2 hours; a steady-state volume of distribution (Vd_{ss}) of approximately 118 L, and an estimated clearance of approximately 39 L/hour. DEX exhibits linear PK in adults in the dosage range of 0.2 to 0.7 µg/kg/hour when administered by IV infusion for up to 24 hours. DEX undergoes extensive hepatic metabolism to inactive metabolites, with 85% undergoing glucuronidation by UDP-glucuronyltransferase (UGT) and 15% by cytochrome P450 2A6.

The PK of DEX has also been characterized in 5 clinical studies in pediatric population mainly in ICU patients. Linear PK was observed in these studies within the dosage ranges (0.2 to 2 µg/kg/hour) evaluated. A population PK (Pop PK) model has been developed to characterize the PK and disposition of DEX in pediatric ICU patients. In this model, a total of 1372 plasma DEX concentration records from 131 pediatric ICU patients of age range 0.01 to 17 years enrolled in 4 studies (Study DEX-09-08, CHOP study, Study DEX-08-01, and Study DEX-11-01) were used for the analyses. The final population PK model was a 2-compartment model with inter individual variability estimated on clearance (CL), inter-compartmental clearance (Q), volume of the central compartment (Vc), and volume of the peripheral compartment (Vp) using exponential error models, fixed allometric exponents on the clearance (0.75 for CL and Q) and volume of distribution (1.0 for Vc and Vp) parameters.

Limited information is available about the PK of DEX in pediatric procedural sedation (PPS) patients. However, based on the known clearance pathways of DEX, the disposition of DEX in PPS patients is assumed to be similar to that in pediatric ICU patients, which seems to be supported by the reported PK parameters of DEX by Vilo et al (2008)[13] in PPS patients compared to the PK parameters (CL and Vd_{ss}) obtained from pediatric ICU population PK model, as shown in Table 1 below. As such, the PK profiles of DEX in PPS patients at the proposed doses in this study are simulated by using the pediatric ICU population PK model (Cognigen Corporation. Population Pharmacokinetic Evaluation of Dexmedetomidine Infusion in Mechanically Ventilated Pediatric Subjects. June 6, 2012, Report on file). These simulation results are provided for information purposes only.

Table 1. Reported DEX PK Parameters in Pediatric ICU Patients and Pediatric Procedural Sedation Patients

Pediatric Patients	Median Age (years)	CL (L/h/kg)	Vd_{ss} (L/kg)
ICU*	1.31	1.11	2.42
Procedural Sedation[13]	0.6	1.04	3.8
	4.2	1.04	2.2

Source: *Cognigen Pop-PK model
Abbreviations: CL = Clearance; DEX = Precedex; ICU = Intensive Care Unit; Vd_{ss} = Volume of Distribution at Steady State

Methods

Assumptions

- Similar PK profiles of DEX between PICU patients and PPS patients.
- Linear PK of DEX in the dose range from 0.5 to 2.0 µg/kg when administered via IV infusion.

Software

The PopPK simulations were conducted using the software packages NONMEM, version 7.2 (ICON Development Solutions, Hanover, MD). A statistical software package R version 3.2.2 (R Development Core Team) and R studio (RStudio, Inc.) was used for generation of simulation input datasets, statistical analysis and creation of simulation output graphs for this protocol. Non-compartmental analysis to estimate the PK parameters were conducted using Phoenix WinNonlin, version 6.4 (Certara USA, Inc., Princeton, NJ).

Input Datasets

Individual PK parameter and demographic information (age, body weight and sex) from the pediatric ICU population PK model were used as input parameters for the simulations. There were total 124 pediatric subjects in the final ICU population PK model. Out of those 124 subjects, 28 subjects were less than 1 month old and were thus excluded from simulation input file. Age and body weight distribution for the remaining 96 subjects based on age category proposed in protocol C0801039 are provided in Table 2 below. The proposed loading and maintenance doses for each age group (Table 3 and Table 4 below) were used as dose level inputs for the simulations employing the final pediatric ICU population PK model.

Table 2. Demographics of Input Dataset by Age Group

Demographics	Group-1 (1 month to < 2 years)	Group-2 (2 to ≤ 12 years)	Group-3 (12 to ≤ 17 years)
N	42	44	10
Age Range (Years)	0.099 – 1.766	2.07 - 11.63	12.07 - 16.97
Mean Body Weight (Kg)	7.78	19.95	45.63
Body Weight Range (Kg)	3.15 – 13.5	9.98 - 61.6	23.59 - 72.3

Source: ePharm Artifact ID: 14554510

Table 3. Dose levels for Subjects >2 years of age

	Loading Dose (µg/kg)	Maintenance Infusion Dose (µg/kg/hour)
Low dose	0.5	0.5
Middle dose	1.2	1.0
High dose	2.0	1.5

Table 4. Dose levels for Subjects ≥1 month to ≤2 years of age

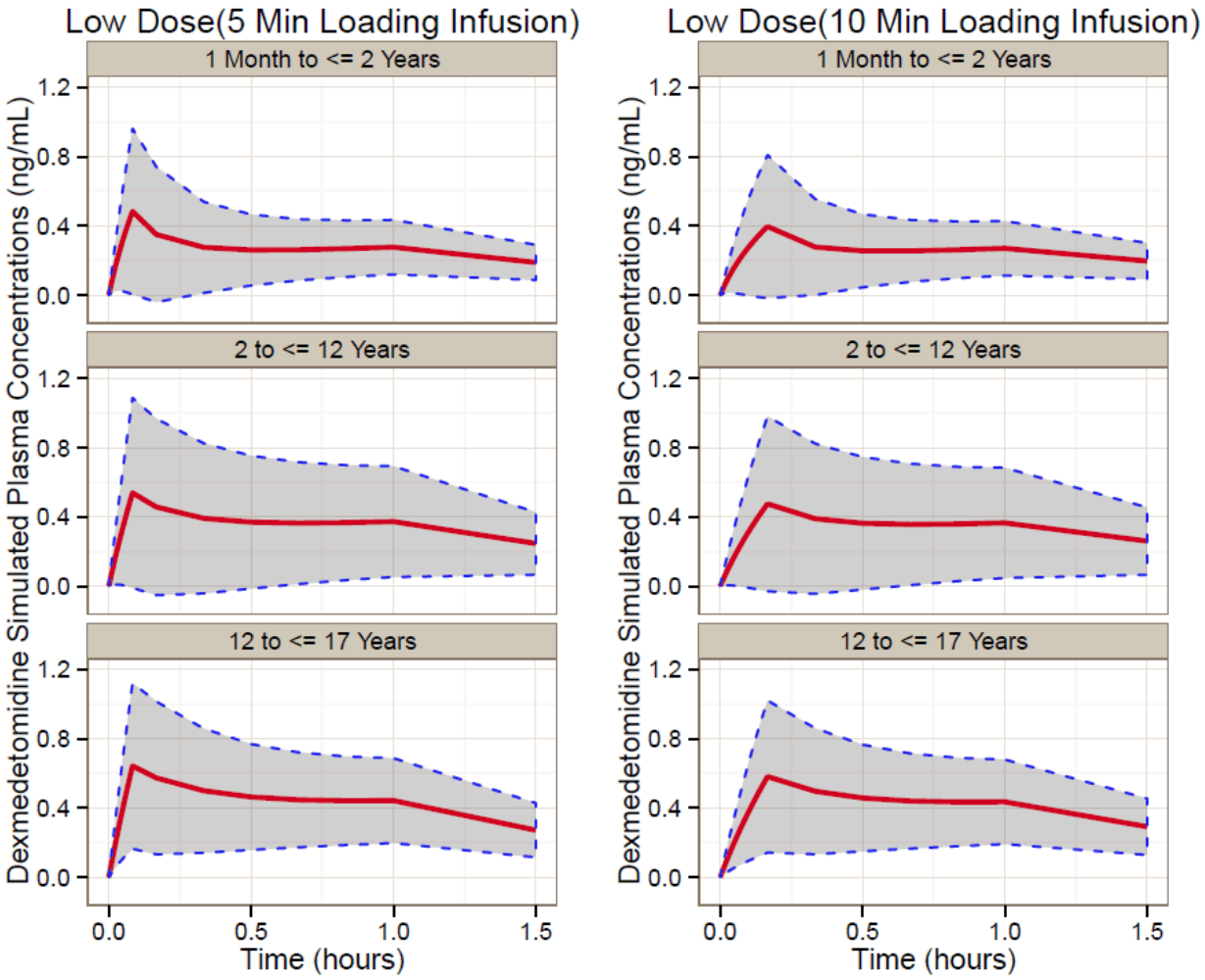
	Loading Dose (µg/kg)	Maintenance Infusion Dose (µg/kg/hour)
Low dose	0.5	0.5
Middle dose	1.0	1.0
High dose	1.5	1.5

Results

Simulation Outputs

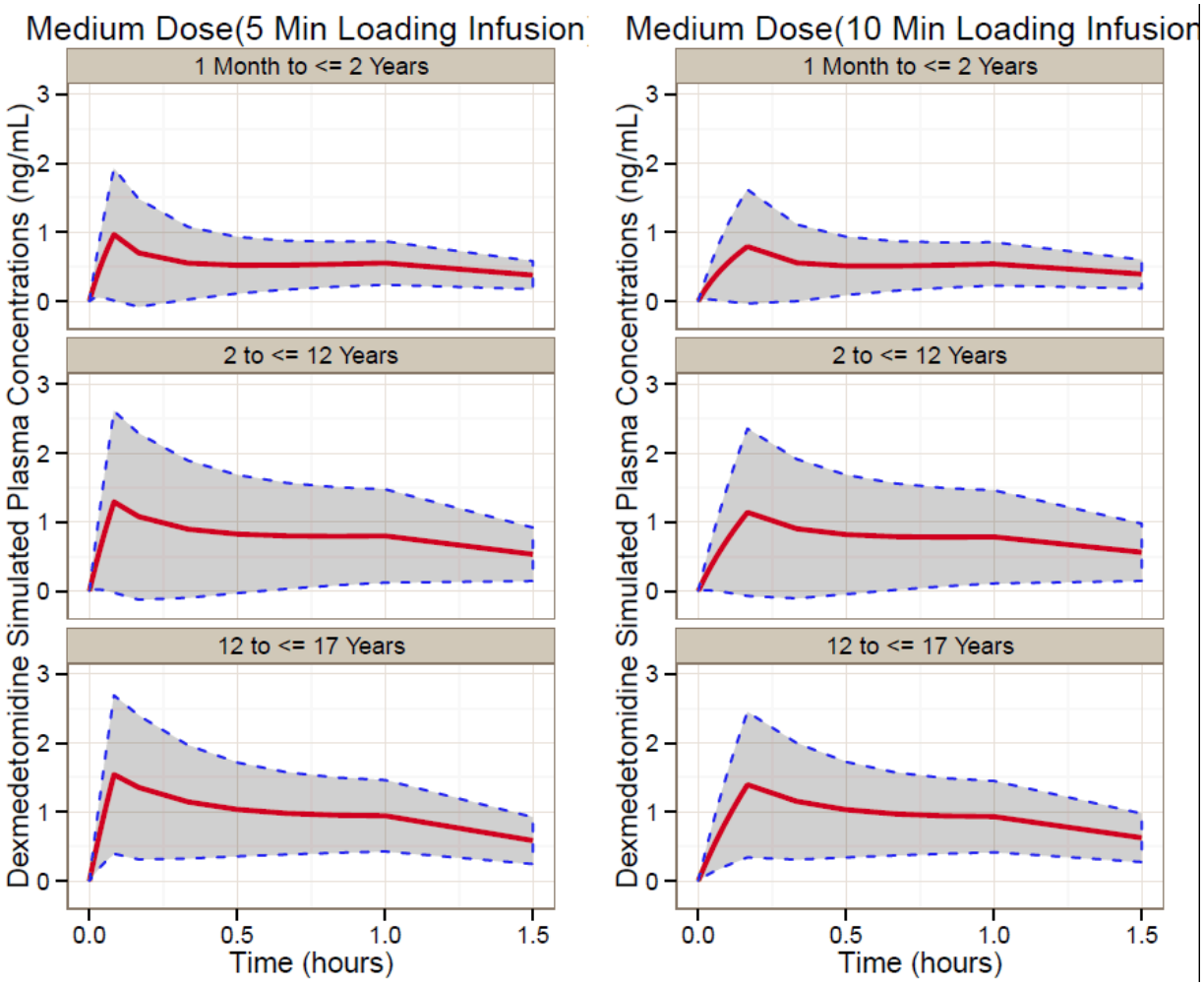
The simulated plasma DEX concentration-time profiles for each age group at low, mid and high dose levels are presented in Figure 1, Figure 2, and Figure 3, respectively. The PK profiles of DEX via either a 5-minute or 10-minute loading dose infusion are also graphically presented side-by-side in the same graph for comparison. The PK profiles of DEX via 5 min and 10 min infusion are generally similar within each age group at same dose except that the peak levels of DEX are slightly higher via 5 min loading infusion than that via 10 min loading infusion.

Figure 1. Simulated Plasma Dexmedetomidine Concentration vs Time Profiles in Different Age Groups following Low Dose Infusion



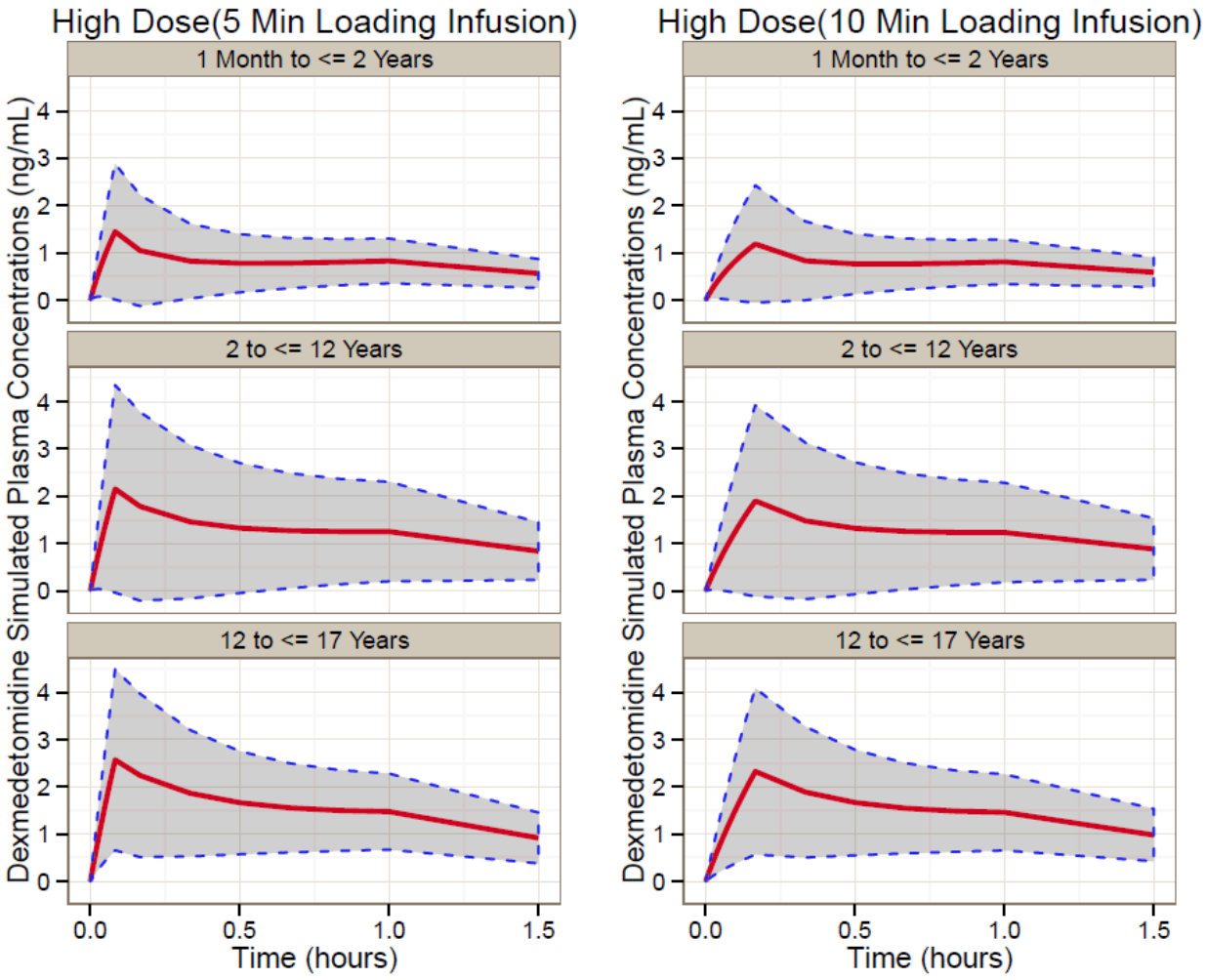
Red line: Mean concentration
Shaded gray area: 90 % confidence interval.
Source data: ePharm Artifact ID: 14067909

Figure 2. Simulated Plasma Dexmedetomidine Concentration vs Time Profiles in Different Age Groups following Medium Dose Infusion



Red line: Mean concentration
Shaded gray area: 90 % confidence interval.
Source data: ePharm Artifact ID: 14068066

Figure 3. Simulated Plasma Dexmedetomidine Concentration vs Time Profiles in Different Age Groups following High Dose Infusion



Red line: Mean concentration
Shaded gray area: 90 % confidence interval.
Source data: ePharm Artifact ID: 14068080

Simulated PK Parameters

PK parameters including area under plasma concentration time curve (AUC) and maximum plasma concentrations (Cmax) for simulated DEX data were estimated by noncompartmental PK analysis of simulation output. Summary of PK parameters for each age group at low, medium and high dose levels are presented in Table 5.

Table 5. Dexmedetomidine PK Parameters for Simulated Data by Dose and Age Group

Dose Level	Age Group	PK Parameters	5 Minute Loading Infusion		10 Minute Loading Infusion	
			N	Mean (SD)	N	Mean (SD)
Low Dose	1 Month to ≤2 Years	AUC_{0-t} (ng*h/mL)	42	0.381(0.154)	42	0.352 (0.142)
		C_{max} (ng/mL)	42	0.453 (0.259)	42	0.408 (0.242)
	2 to ≤12 Years	AUC_{0-t} (ng*h/mL)	44	0.513 (0.285)	44	0.475 (0.264)
		C_{max} (ng/mL)	44	0.517 (0.291)	44	0.496 (0.292)
	12 to ≤17 Years	AUC_{0-t} (ng*h/mL)	10	0.621 (0.223)	10	0.574 (0.206)
		C_{max} (ng/mL)	10	0.603 (0.248)	10	0.595 (0.248)
Medium Dose	1 Month to ≤2 Years	AUC_{0-t} (ng*h/mL)	42	0.761 (0.309)	42	0.704 (0.283)
		C_{max} (ng/mL)	42	0.906 (0.517)	42	0.816 (0.484)
	2 to ≤12 Years	AUC_{0-t} (ng*h/mL)	44	1.14 (0.631)	44	1.05 (0.584)
		C_{max} (ng/mL)	44	1.22 (0.703)	44	1.17 (0.711)
	12 to ≤17 Years	AUC_{0-t} (ng*h/mL)	10	1.38 (0.491)	10	1.27 (0.454)
		C_{max} (ng/mL)	10	1.43 (0.607)	10	1.41 (0.614)
High Dose	1 Month to ≤2 Years	AUC_{0-t} (ng*h/mL)	42	1.14 (0.463)	42	1.06 (0.425)
		C_{max} (ng/mL)	42	1.36 (0.776)	42	1.22 (0.726)
	2 to ≤12 Years	AUC_{0-t} (ng*h/mL)	44	1.82 (1.01)	44	1.69 (0.932)
		C_{max} (ng/mL)	44	2.01 (1.18)	44	1.94 (1.20)
	12 to ≤17 Years	AUC_{0-t} (ng*h/mL)	10	2.20 (0.783)	10	2.04 (0.724)
		C_{max} (ng/mL)	10	2.37 (1.02)	10	2.35 (1.04)

Abbreviations: N = Number of subjects; SD = Standard deviation; Cmax = Maximum plasma concentration; AUC_{0-t} = Area under plasma concentration time curve from time zero to time t where t= 1.5 hr.
Source: ePharm Artifact ID: 14067888

CCI [redacted]

Appendix 4. Modified Aldrete Score

The Modified Aldrete Score is an observational scale allowing verbal prompts. The total score is the sum of all values.

Modified Aldrete Score		
ACTIVITY	Able to move 4 extremities voluntarily or on command	2
	Able to move 2 extremities voluntarily or on command	1
	Unable to move extremities voluntarily or on command	0
RESPIRATION	Able to breathe deeply and cough freely	2
	Dyspnea or limited breathing	1
	Apneic	0
CIRCULATION	BP ± 20% of pre-anesthetic level	2
	BP ± 20% to 49% of pre-anesthetic level	1
	BP ± 50% of pre-anesthetic level	0
CONSCIOUSNESS	Fully awake	2
	Arousable on calling	1
	Not responding	0
O_2 SATURATION	Able to maintain O_2 saturation >92 % on room air	2
	Needs O_2 inhalation to maintain O_2 saturation >90%	1
	O_2 saturation <90 % even with O_2 supplement	0

Reference: Aldrete JA. The post-anesthesia recovery score revisited. *Journal of Clinical Anesthesia.* 1995;7:89-91

Appendix 5. Pediatric Anesthesia Emergence Delirium Scale (PAED)

The total PAED score is the sum of all values.

Behavior	Not at all	Just a little	Quite a bit	Very much	Extremely
The child makes eye contact with the caregiver	4	3	2	1	0
The child's actions are purposeful	4	3	2	1	0
The child is aware of his/her surroundings	4	3	2	1	0
The child is restless	0	1	2	3	4
The child is inconsolable	0	1	2	3	4

References: Sikich N, Lerman J. Development and Psychometric Evaluation of the Pediatric Anesthesia Emergence Delirium Scale. *Anesthesiology* 2004; 100:1138–45 and Bajwa S, Fanzca D, Cyna A. A Comparison of Emergence Delirium Scales Following General Anesthesia in Children. *Pediatric Anesthesia*. 2010; 20(8): 704-711.

Appendix 6. Pediatric Sedation State Scale (PSSS)

State	Behavior
5	Patient is moving (purposefully or nonpurposefully) in a manner that impedes the proceduralist and requires forceful immobilization. This includes crying or shouting during the procedure, but vocalization is not required. Score is based on movement.
4	Moving during the procedure (awake or sedated) that requires gentle immobilization for positioning. May verbalize some discomfort or stress, but there is no crying or shouting that expresses stress or objection.
3	Expression of pain or anxiety on face (may verbalize discomfort), but not moving or impeding completion of the procedure. May require help positioning (as with a lumbar puncture) but does not require restraint to stop movement during the procedure.
2	Quiet (asleep or awake), not moving during procedure, and no frown (or brow furrow) indicating pain or anxiety. No verbalization of any complaint.
1	Deeply asleep with normal vital signs, but requiring airway intervention and/or assistance (eg, central or obstructive apnea, etc).
0	Sedation associated with abnormal physiologic parameters that require acute intervention (ie, oxygen saturation <90%, blood pressure is 30% lower than baseline, bradycardia receiving therapy).

Reference: Cravero JP, Askins N, Sriswasdi P, et al. Validation of the Pediatric Sedation State Scale. *Pediatrics.* 2017; 139(5):e20162897

Appendix 7. HR and RR Centile Chart Cut-offs for Children from Birth to 18 Years of Age

Source: Fleming S, Thompson M, Stevens R, et al. Normal ranges of HR and RR in children from birth to 18 years of age: a systematic review of observational studies. *Lancet.* 2011; 377:1011-18, Web appendix.

Web Table 4: Proposed respiratory rate cut-offs (breaths/minute) based on centile charts

Age Range	1st centile	10th centile	25th centile	Median	75th centile	90th centile	99th centile
0 – 3m	25	34	40	43	52	57	66
3 – 6m	24	33	38	41	49	55	64
6 – 9m	23	31	36	39	47	52	61
9 – 12m	22	30	35	37	45	50	58
12 – 18m	21	28	32	35	42	46	53
18 – 24m	19	25	29	31	36	40	46
2 – 3y	18	22	25	28	31	34	38
3 – 4y	17	21	23	25	27	29	33
4 – 6y	17	20	21	23	25	27	29
6 – 8y	16	18	20	21	23	24	27
8 – 12y	14	16	18	19	21	22	25
12 – 15y	12	15	16	18	19	21	23
15 – 18y	11	13	15	16	18	19	22

Age ranges given in years (y) and months (m).

Web Table 5: Proposed heart rate cut-offs (beats/minute) based on centile charts

Age Range	1st centile	10th centile	25th centile	Median	75th centile	90th centile	99th centile
Birth	90	107	116	127	138	148	164
0 – 3m	107	123	133	143	154	164	181
3 – 6m	104	120	129	140	150	159	175
6 – 9m	98	114	123	134	143	152	168
9 – 12m	93	109	118	128	137	145	161
12 – 18m	88	103	112	123	132	140	156
18 – 24m	82	98	106	116	126	135	149
2 – 3y	76	92	100	110	119	128	142
3 – 4y	70	86	94	104	113	123	136
4 – 6y	65	81	89	98	108	117	131
6 – 8y	59	74	82	91	101	111	123
8 – 12y	52	67	75	84	93	103	115
12 – 15y	47	62	69	78	87	96	108
15 – 18y	43	58	65	73	83	92	104

Age ranges given in years (y) and months (m).
"Birth" refers to the immediate neonatal period.

Appendix 8. Normal Vital Signs According to Age

Table 67-1, Nelson Textbook of Pediatrics

AGE	HEART RATE (beats/min)	BLOOD PRESSURE (mm Hg)	RESPIRATORY RATE (breaths/min)
Premature	120 – 170*	55-75 / 35-45†	40-70‡
0-3 months	100-150*	65-85 / 45-55	35-55
3-6 months	90-120	70-90 / 50-65	30-45
6-12 months	80-120	80-100 / 55-65	25-40
1-3 years	70-110	90-105 / 55-70	20-30
3-6 years	65-110	95-110 / 60-75	20-25
6-12 years	60-95	100-120 / 60-75	14-22
12+ years	55-85	110-135 / 65-85	12-18

Source: Nelson Textbook of Pediatrics, 20th Ed, 2016

* In sleep, infant heart rates may drop significantly lower, but if perfusion is maintained, no intervention is required.

† A blood pressure cuff should cover approximately two-thirds of the arm; too small a cuff yields spuriously high blood pressure readings, and too large a cuff yields spuriously low pressure readings.

‡ Many premature infants require mechanical ventilatory support, making their spontaneous respiratory rate less relevant.

Appendix 9. Propofol Pre-filled Syringe Medical Device Reporting in Japan

Propofol pre-filled syringe medical device incidents in Japan including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator to the Sponsor throughout the study.

The detection and documentation procedures described in this protocol apply **only** to sites in Japan using Propofol pre-filled syringes in the study.

The specific reporting procedure process for medical device incidents will be provided to the sites in Japan under separate cover.

Definitions of a Medical Device Incident

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health. • Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of healthcare personnel.

It is sufficient that:

- An **incident** associated with a device happened.

AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness;
- Permanent impairment of body function or permanent damage to body structure;
- Condition necessitating medical or surgical intervention to prevent one of the above;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

Examples of Incidents

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's study intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documentation

- Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice.
- For medical device incidents meeting the definition of an AE or an SAE, the appropriate AE CRF page will be completed. An SAE will also require completion of the CT SAE form which will be forwarded to Pfizer Safety as per Section 8.1 of the protocol.
- All medical device incidents must be reported to the manufacturer by the site.
- The results from the manufacturer's investigation of the medical device incident must also be reported to the sponsor as an appendix to the original report, as appropriate.
- It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.