Protocol: C0801039

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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

Statistical Analysis Plan
(SAP)

Version: 2

Date: 09June2021

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

- Status of study when amendment (version 2) made: Study Ongoing
- Descriptions of and rationale for the changes:

Details of the Changes	Rationale for the Changes
Section 2.1. 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.	Updates are made to be consistent with protocol amendment 1.
Section 2.1 Primary Endpoint: revised the primary efficacy endpoint to clarify the comparison is in the combined age cohorts	Updates are made to be consistent with protocol amendment 2.
Section 2.1 Endpoint: Secondary Efficacy: Percent of time at the target sedation rating scale score revised to: Percent of time at the target sedation rating scale score (Pediatric Sedation State Scale [PSSS] rating of 2) during the DEX maintenance infusion.	Clarified the percent of time at the target sedation during DEX maintenance infusion to be analyzed.
Section 2.1 Endpoint: Safety: corrected the safety endpoint to include subjects who require intervention to complete the MRI; changed the protocol-specified AE term “systolic hypotension”to “hypotension”	Updates are made to be consistent with protocol amendment 2.
Section 2.2. Study Design Table 1 Schedule of Clinical Activities updated as appropriate to be consistent with the protocol amendment 2.	Updates are made to be consistent with protocol amendment 2.
Section 2.3. Sample Size Determination: revised to remove trailing zeroes related to DEX dosing.	Updates are made to be consistent with protocol amendment 1.
Section 3.2. Secondary Efficacy Endpoint(s) – Emergence Time: revised to: Subjects who are withdrawn or discharged without reaching an Aldrete score $\geqslant$9, will be considered as having censored time computed from end of	The censored time for emergence time is clarified.

MRI scan to time of the last clinical assessment (vital signs). Zero minute will be used as the censored time if no vital signs are taken during the post-MRI recovery period.	
Section 3.5.4 Other Safety Endpoints revised to: corrected a safety endpoint and revised to : Percent of subjects who completed the MRI scan and required artificial ventilation or intervention to restore baseline or normal hemodynamic status.	Corrected to include subjects who require intervention to complete the MRI per protocol amendment 2.
Section 3.5.4. Other Safety 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.	Updates are made to be consistent with protocol amendment 1.
Section 3.5.4. Other Safety Endpoints: revised to: remove "All interventions used by the anesthesiologist to preserve hemodynamic stability will be compiled. Treatments for hypertension, tachycardia, hypotension, bradycardia, and respiratory depression will be descriptively summarized by each dose level and age cohort."	The hemodynamic stability is removed from the protocol amendment 1.
Section 6.2.2 Percentage of Time at the Target Sedation Scale, ADD: In addition, the difference between dose levels in the percentage of time at Pediatric Sedation State Scale [PSSS] rating of 2 or 3 during the DEX maintenance infusion will be assessed. The percentage of time at target Pediatric Sedation State Scale [PSSS] rating of 2 during the DEX maintenance infusion with/ without PRO will be summarized as well.	Additional analyses are added.
Section 6.2.3 Amount of Time to First PRO ADD: Kaplan Meier plot of time from the start of DEX loading dose infusion to the time of first PRO bolus Infusion will be performed by dose level and age cohort.	Kaplan Meier Plots are added.

Section 6.2.4 Emergence Time, ADD: Kaplan Meier plot of emergence time by dose level and age cohort will be performed.	Kaplan Meier Plots are added.
Section 6.6.5. Electrocardiograms: revised to Electrocardiograms and MRI scan; add "Duration of MRI will be summarized descriptively by dose level and age cohort."	The duration of MRI will be reported in the CSR.

2. INTRODUCTION

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 in the United States (US) and Japan.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C0801039. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives and Endpoints

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.

[redacted]

- 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) 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.

[redacted]

- Safety:
  - Incidence, seriousness, causality and severity of treatment-emergent adverse events (TEAE).
  - Percent of subjects who complete 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 (AE) 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 AEs after discontinuation of DEX infusion.

2.2. 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 in the US and Japan. The sponsor, subject and investigator will be blinded to the dose of DEX.

This study includes a Day 1, Day 2 Follow-up and Day 29 Long-term Follow-up Visit. The Day 1 Visit is comprised of a Screening (pre-randomization) Phase, 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) as shown below:

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 Screening Visit procedures and pre-randomization procedures at the Day 1 Period 1 Visit, subjects 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 (e.g., 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 PI clinical judgment. The target sedation level is indicated by a PSSS score of 2. Subjects will also be administered supplemental IV fluids throughout the DEX infusion at a maintenance rate per the protocol

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.

The schedule of activities Table 1 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, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1 Schedule of Clinical Activities

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		
[redacted] CCI			[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 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 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 the Protocol 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 the Protocol 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 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 the Protocol 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 the Protocol Section 5, Study Treatments.

2.3. 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, i.e. 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 year and ≥2 years to <17 year. The table below shows the planned enrollment in this study.

Table 2 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 (1). 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.

3. ENDPOINTS AND BASELINE VARIABLES

3.1. Primary and Key Secondary Efficacy Endpoint(s)

- 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.

A subject who does not complete the MRI scan will be considered a treatment failure, i.e., the subject will be counted as receiving PRO and will not be counted as a successful responder for the percentage of subjects who do not require concomitant PRO. An indicator variable for the use of PRO after the first dose of DEX or during MRI scan is defined as follows:

= 1, if the subject does not require PRO during DEX administration or during the MRI scan

= 0, if the subject does require PRO during DEX administration or during the MRI scan or does not complete the MRI scan

The method for the primary endpoint will be repeated for the key secondary endpoint for each age cohort.

3.2. Secondary Efficacy Endpoint(s)

- 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. The method for the primary endpoint will be repeated for these comparisons.

- Percent of time at the target sedation rating scale score (Pediatric Sedation State Scale [PSSS] rating of 2) during the DEX maintenance infusion.

The PSSS rating scale is shown in Table 3. The percentage of subjects in the PSSS assessment will be derived as a ratio of the time during which the target sedation rating scale score is met (PSSS=2) during the DEX maintenance infusion to the total time while DEX is administered as a continuous infusion during the maintenance infusion.

Table 3 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 (e.g., central or obstructive apnea, etc.).
0	Sedation associated with abnormal physiologic parameters that require acute intervention (i.e., oxygen saturation <90%, blood pressure is 30% lower than baseline, bradycardia receiving therapy).

- The amount of time from the start of the DEX loading dose infusion to the time of the first PRO bolus administration.

  Subjects who do not have PRO administered will be considered censored. Censored time to first dose of PRO will be computed as length of time from the onset of the DEX loading dose infusion up to the time the DEX infusion is stopped. For analyses of this time-to-event efficacy variable an indicator variable will be derived as follows:

  = 1, if subject receives PRO

  = 0, if censored (does not receive PRO).

- Emergence time (defined as the time from the end of the MRI scan to when the subject meets a Modified Aldrete score ≥9).

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

- The proportion of subjects at each dose level who receive PRO.

  The number and percentage of subjects who receive PRO will be summarized from the end of the DEX loading dose to the end of the MRI scan.

- Total amount (mcg/kg) and weight and time adjusted amount (per kg per minute basis) of concomitant PRO required to successfully complete the MRI scan.

  The number of bolus doses, average infusion rate (mcg/kg/min), total dose of PRO received (mcg/kg), and duration of PRO infusion will be summarized.

CCI [redacted]

3.4. Baseline Variables

The baseline assessment is defined as the last assessment recorded before study drug administration. The following baseline assessments will be summarized.

- Vital signs (HR, BP, MAP, RR)
- Body Temperature
- PSSS
- Prior Medications

3.5. Safety Endpoints

The main safety endpoints are incidence, seriousness, causality and severity of TEAEs. General adverse event (AE) summaries are described in Section 3.5.1, protocol-specified AEs are presented in Section 3.5.2 and other safety endpoints are listed in Section 3.5.4.

3.5.1. Adverse Events

The MedDRA adverse event dictionary (most recent, available version at the time of study initiation) will be used to map AEs to preferred terms and system organ classes. A TEAE is defined as an AE that emerges or worsens relative to the pre-treatment state during the time from the start of study treatment on DAY 1 through DAY 2. Only TEAEs will be analyzed. However, all AEs will be presented in data listings.

An overall summary of TEAEs across the study drug period and up to the end of Day 2 will be generated. TEAEs will be summarized separately for 3 different periods (loading dose, maintenance dose infusion, post study treatment). An AE occurring during a study treatment period (loading dose period and/ or maintenance period), is defined as any AE with new onset during that period or worsening relative to the period prior to start of DEX treatment. An AE occurring post study drug is defined as any AE with new onset or worsening relative to the period prior to DEX treatment, any time after study drug discontinuation through Day 2.

For summaries by severity, if a subject has multiple events occurring in the same system organ class (SOC) or same preferred term, then the event with the highest severity will be summarized. Any AE with a missing severity will be summarized as severe.

Relationship to study drug will be summarized as follows:

- Related (includes definitely related, probably related and possibly related)
- Not Related (includes probably not related and not related)

3.5.2. Protocol-Specified Adverse Events

3.5.2.1. Changes in Blood Pressure and Heart Rate

Blood pressure and heart rate will be assessed throughout the study, and blood pressure and heart rate measurements exceeding specified limits defined in Section 8.4.1.1 of the C0801039 protocol will be recorded as AEs. These AEs include: bradycardia, hypotension, and hypertension. Since the study has pre-specified absolute and relative thresholds for these AEs, the AE data will be used to determine the incidence of cardiac AEs. Further analysis will be applied to those cardiac AEs that require intervention, where the number and percentage of subjects who received interventions to preserve cardiac function will be summarized as well as the interventions that were received.

3.5.2.2. 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 (e.g., 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 and will be summarized.

3.5.2.3. 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 Section 8.4.1.3 of the protocol will be recorded as adverse events. These adverse events include bradypnea, hypoxia and apnea. Since the study has pre-specified absolute and relative thresholds for these AEs, the AE data will be used to determine the incidence of respiratory depression. Further analysis will be applied to respiratory depression that requires intervention, where the number and percentage of subjects who received interventions to preserve respiratory function will be summarized as well as the interventions received.

3.5.3. 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 the protocol and will be handled as SAEs in the safety database.

3.5.4. Other safety endpoints

- Mean change from baseline in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) and respiratory rate (RR).

  The post baseline value will be at the timepoint closest to the time for the planned time period.

- Percent of subjects who complete the MRI scan and required artificial ventilation or intervention to restore baseline or normal hemodynamic status.

  An indicator variable for subjects who complete the MRI scan with or without the need for artificial ventilation or intervention is defined as follows:

  = 1, if the subject did not need artificial ventilation or intervention

  = 0, if the subject did need artificial ventilation or intervention.

  All interventions used by the anesthesiologist to preserve hemodynamic stability will be compiled. Treatments for hypertension, tachycardia, hypotension, bradycardia, and respiratory depression will be descriptively summarized by each dose level and age cohort.

- Time outside of the stable range for hemodynamic parameters of SBP and HR.

  The time outside of the stable range for hemodynamic parameters will be assessed as defined below:

  Hemodynamic stability is characterized by maintenance of (1) the SBP within + 30% of pre-study drug baseline, and (2) HR within + 30% of pre-study drug baseline. A composite endpoint of the time outside of the hemodynamically stable range will be constructed as such:

$$\frac{\text{[SBP time outside range] + [HR time outside range]}}{\text{Duration of study drug infusion period}}$$

The numerator will be the time outside of the stable range for each hemodynamic parameter during the time period of evaluation. The time outside of the stable range will be summed for each parameter and divided by the denominator. The denominator will be the time from onset of study drug infusion to the time study drug is discontinued. Theoretically, values for this endpoint could range from 0 (the subject remains within range during the time period of evaluation on all parameters assessed) to 2.0 (subject was out of range for the time period of evaluation for both SBP and HR). Linear extrapolation will be used to estimate the parameter values between observation points.

- Incidence of DEX withdrawal-related adverse events after discontinuation of the DEX infusion through Day 2.

  The number and percent of subjects who have withdrawal symptoms reported as AEs, such as agitation/anxiety, nausea, (rebound) tachycardia and (rebound) hypertension will be tabulated. These are defined as AEs with new onset after study treatment discontinuation or worsening relative to the treatment period.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all participants will be assessed to determine if participants meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

4.1. Enrolled Population (EP)

All participants who sign the informed consent document.

4.2. Safety Analysis Set

The safety analysis set consists of all randomized subjects who receive 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 are 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.

4.3. 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 are randomized. This will be the primary population for efficacy analysis.

4.4. Efficacy Evaluable Population (EEP)

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

4.5. Per Protocol Population (PPP)

All subjects included in the FAS and have no major protocol deviations will form the PPP.

4.6. Japanese Population Set (JPS)

All randomized Japanese subjects who receive any amount of DEX.

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.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The hypothesis that will be tested in this study is

$$H_0: p_1 - p_2 = 0$$

$$H_1: p_1 - p_2 \neq 0$$

where p_1 and p_2 are the proportion of subjects who do not require concomitant PRO to complete the MRI for the high and low dose respectively.

The high dose level will be considered superior to the low dose level with respect to the proportion of subjects who do not require concomitant PRO to complete the MRI if the difference is statistically significant in favor of the high dose level at the 2-sided 0.05 level.

5.2. General Methods

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

For continuous variables, N, mean, median, SD, minimum, Q1, Q3 and maximum will be presented. The mean and median will be displayed to one decimal place more than the raw value. The standard deviation will be displayed to two decimal places more than the raw value.

For categorical variables, N and percent will be shown. All percentages will be reported to one decimal place.

Subject listings of all data from the CRFs will be presented.

5.3. Methods to Manage Missing Data

In general, missing data will not be imputed, exceptions will be described in the SAP.

5.4. Time points

Screening/Pre-Study Drug Administration Period: The period before randomization.

Baseline: The last non-missing data prior to study drug administration.

Study Drug Administration Period: Treatment Period (DEX loading dose and continuous infusion).

Day 1: The visit is comprised of 3 phases: a Screening (pre-randomization) Phase, a Period 1 (MRI scan) Phase and a Period 2 (Post-MRI Recovery) Phase.

Day 2: The visit is a 24-hour (±2 hours) follow-up after discontinuing the study drug infusion.

Day 29: The visit is a 28 day (+3 days) long term follow-up visit.

Post-Study Drug Administration Period: time after discontinuing the study drug infusion.

6. ANALYSES AND SUMMARIES

6.1. Primary and Key Secondary Endpoint(s)

6.1.1. Primary Endpoint

The DEX high vs low dose group will be compared by Mantel-Haenszel test in PROC FREQ. The difference between high and low dose groups will be assessed using odds ratios and 95% confidence intervals on the odds ratio. Additionally, 95% confidence interval on the percent of subjects not requiring supplemental PRO will be provided by dose level using exact 95% confidence intervals. 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, PPP and JPS.

6.1.2. 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, PPP, and JPS.

6.2. Secondary Endpoint(s)

All secondary endpoints will be summarized overall and by age cohort for the FAS and JPS.

6.2.1. Percentage of Subjects Not Required PRO at the middle dose level

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.

6.2.2. Percentage of Time at the Target Sedation Scale

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

In addition, the difference between dose levels in the percent of time at the PSSS rating of 2 or 3 during the DEX maintenance infusion will be assessed using the Wilcoxon test.

The percent of time at the target PSSS rating of 2 during the DEX maintenance infusion with/ without PRO will be summarized by dose level and age cohort as well.

6.2.3. Amount of Time to First PRO

The time to first dose of concomitant PRO will be summarized with Kaplan-Meier estimates. Between dose groups comparisons will be made with log-rank tests.

Kaplan Meier plot of time from the start of DEX loading dose infusion to the time of first PRO bolus Infusion will be performed by dose level and age cohort.

6.2.4. Emergence Time

Time (minutes) from completion of MRI to time a subject first receives an Aldrete score of 9 or greater will be summarized using the Kaplan-Meier method. Between dose groups comparisons will be made with log-rank test.

Kaplan Meier plot of emergence time by dose Level and age cohort will be performed.

6.2.5. Total amount and weight and time adjusted amount of concomitant PRO

The total amount (mcg/kg) and the average infusion rate (mcg/kg/min), number of boluses and duration of PRO given for sedation will be summarized for each dose level with descriptive statistics (N, mean, SD, median, min, Q1, Q3, and max). The difference between dose groups (high dose and low dose, and medium dose and low dose and high dose versus medium dose) will be assessed using analysis of variance (ANOVA) when assumption of normal distribution is reasonable or by nonparametric tests when this assumption is not met.

CCI [redacted]

[redacted]

[redacted]

6.4. Subgroup Analyses

No additional subgroup analysis is planned other than JPS. All efficacy and safety endpoints will be analyzed by age cohort and for the JPS.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

The baseline and demographics will be descriptively summarized by dose level for FAS, JPS, and Safety populations, overall and by age cohort. For categorical variables (sex, race, etc.) counts and percentages of subjects will be displayed. For continuous variables (age, weight, height, etc.), N, mean, SD, median, min, Q1, Q3, max will be computed.

Temperature given in Fahrenheit will be converted to Celsius using the formula: C = (5/9)*(F-32).

6.5.2. Disposition of Subjects

The number and percentage of subjects enrolled and who completed the study will be summarized descriptively in each dose level and age cohort.

The number and percentage of subjects discontinuing study drug prematurely and reasons for discontinuation will be summarized (N and percent) by dose level and each age cohort.

6.5.3. Study Treatment Exposure

The length of time on study drug DEX will be summarized descriptively for each dose level and age cohort, also the number and percentage of subjects exposed to study drug during the treatment period will be summarized (N and percent) by time of exposure for the loading

dose, maintenance dose, and total duration. Total duration of exposure to study drug (min), is equal to total duration of loading dose plus total duration of maintenance dosing.

Exposure to study drug will not be adjusted for dose interruptions. Loading dose will be summarized using actual dose received.

Maintenance dose will be summarized through the following parameters:

- Total dose infused (mcg/kg) which is equal to the sum of all maintenance dose infusion rate (mcg/kg/min) times duration of the maintenance dose infusion (min)
- Average dose (mcg/kg/min) which is equal to total dose of study drug infused (mcg/kg) divided by total duration of dosing (min)

Total dose received (mcg), which is equal to total dose of study drug received (mcg/kg) multiplied by baseline weight (kg);

Total duration of the exposure to study drug (min), which is equal to total duration of loading dose plus total duration of maintenance dosing.

Study treatment exposure will be analyzed for overall subjects and subjects who complete the MRI scan without PRO, and for subjects who complete the MRI scan with PRO use.

6.5.4. Concomitant Medications and Nondrug Treatments

Prior and concomitant medications will be summarized according to WHODRUG Dictionary. The number and percentage of subjects who use prior medications (by preferred term) will be tabulated by dose level/underlying condition/age. The number and percentage of subjects who use concomitant medications will be similarly tabulated. Summaries will be provided overall and by age cohort.

6.6. Safety Summaries and Analyses

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

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.

6.6.1. Adverse Events

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

TEAEs will be analyzed overall and within each period (loading dose period, maintenance dose period, post study treatment through Day 2) according to the Medical Dictionary for

Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. AEs by severity and relationship to study drug will also be summarized, as well as SAEs. Separate tabulations will be displayed for protocol-specified events of bradycardia, hypoxia, apnea, hypotension, hypertension, bradycardia and paradoxical agitation reaction. Additionally, the above AEs, which require medical intervention will also be summarized.

Relative risk of high dose level vs low dose level and medium dose level vs low dose level, and the 95% confidence interval associated with relative risk will be calculated.

The types of individual interventions will be descriptively summarized at each dose level and for each age cohort.

Listings will be presented by subject for all AEs as well as for SAEs, AEs associated with death, and AEs leading to discontinuation of DEX.

6.6.2. Withdrawal Symptoms

Withdrawal symptoms, such as agitation/anxiety, nausea, rebound tachycardia and rebound hypertension will be summarized by each dose level and age cohort. Descriptive summaries will be performed for the incidence of DEX withdrawal-related adverse events after discontinuation of the DEX infusion.

6.6.3. Laboratory Data

Laboratory data at screening will be listed.

6.6.4. Vital Signs

The vital signs included in the safety assessments are SBP, DBP, MAP, HR, RR, and SpO_2.

The absolute value and change from baseline will be summarized descriptively at each timepoint by dose level and age cohort.

Hemodynamic Status

The proportion of subjects who completed the MRI scan without the need for artificial ventilation or intervention to restore baseline or normal hemodynamic status will also be summarized.

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

In addition, descriptive summary statistics will be compiled for the composite endpoint of the time outside of the hemodynamically stable range. Also, the number and percentage of subjects who receive interventions to preserve hemodynamic stability will be summarized for the study drug infusion period and for the post-infusion period, respectively.

6.6.5. Electrocardiograms

ECG data will be listed.

6.6.6. MRI scan

Duration of MRI will be summarized descriptively by dose level and age cohort.

6.6.7. Physical Examination

Physical examination at screening will be listed.

6.6.8. Pediatric Anesthesia Emergence Delirium Scale (PAED).

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

7. INTERIM ANALYSES

No interim analysis is planned.

8. REFERENCES

1. 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.

9. SAS CODES FOR PRIMARY EFFICACY ENDPOINTS

```
proc freq data= efficacy;
tables dose_level*Response /cmh relrisk;
run;
```

Appendix 1. List of Abbreviations

Abbreviation	Term
AE	adverse event
ANOVA	analysis of variance
BPM	beats per minute
BP	blood pressure
CRF	case report form
CSR	clinical study report
DBP	diastolic blood pressure
DEX	dexmedetomidine
ECG	electrocardiogram
$EtCO_2$	end-tidal carbon dioxide
EP	enrolled population
FAS	full analysis set
FDA	Food and Drug Administration (United States)
ITT	intent-to-treat
KG	kilogram
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
PAED	Pediatric Anesthesia Emergence Delirium Scale
PE	Physical examination
PI	principal investigator
PPP	per-protocol Population
PSSS	Pediatric Sedation State Scale
PT	preferred term
PREA	Pediatric Research Equity Act
PRO	propofol
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SpO_2	saturation of peripheral oxygen
TEAE	treatment-emergent adverse event
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary