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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME:
Precedex® / Dexmedetomidine

PROTOCOL NO.: C0801017 (ZIN-DEX-1506)

PROTOCOL TITLE:

Phase 3, Multi-Center, Single-Arm, Open-Label Study Evaluating the Efficacy, Safety, and Pharmacokinetics of DA-9501 (Dexmedetomidine Hydrochloride) in Pediatric Subjects in the Intensive Care Unit

Study Centers: Twelve (12) centers in Japan took part in the study.

Study Initiation and Final Completion Dates:

20 July 2016 and 24 May 2017

Phase of Development:

Phase 3

Study Objective:

To evaluate the efficacy, safety, and pharmacokinetic (PK) of dexmedetomidine given as continuous intravenous (IV) infusion in pediatric subjects (≥45 weeks corrected gestation age [CGA] to <17 years old) requiring sedation under intensive care.

METHODS

Study Design:

This study was a Phase 3, multi-center, single-arm, open-label study with the objective of evaluating the efficacy, safety and PK of dexmedetomidine when given as a continuous IV infusion in pediatric subjects ≥45 weeks CGA to <17 years old. Based on the indications for dexmedetomidine in adults, the subject population was set to be "pediatric subjects requiring sedation during and after mechanical ventilation in intensive care." Also, according to a questionnaire survey in pediatric intensive care physicians, there were some cases of the use of dexmedetomidine in subjects aged <45 weeks CGA, but in these ages, usual sedative was not used or dexmedetomidine was not the first choice even when sedation was required and the main target subjects were considered to be subjects aged ≥45 weeks CGA; and therefore, the target age was set to be ≥45 weeks CGA to <17 years old.

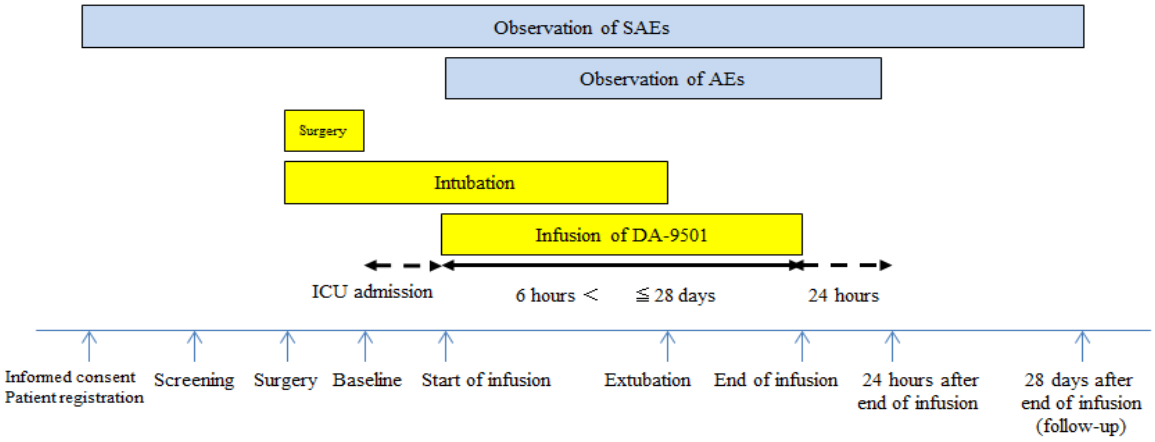
It was considered that there would be subjects requiring sedation in both surgical subjects and medical intensive care unit (ICU) subjects, and therefore it was made possible to enroll

both subject populations, and the target study population was set to be "pediatric subjects undergoing mechanical ventilation management under intensive care and requiring sedation (age ≥45 weeks CGA to <17 years old)".

Note: Although PK was included as a study objective, it was an exploratory objective and details are not presented in this document.

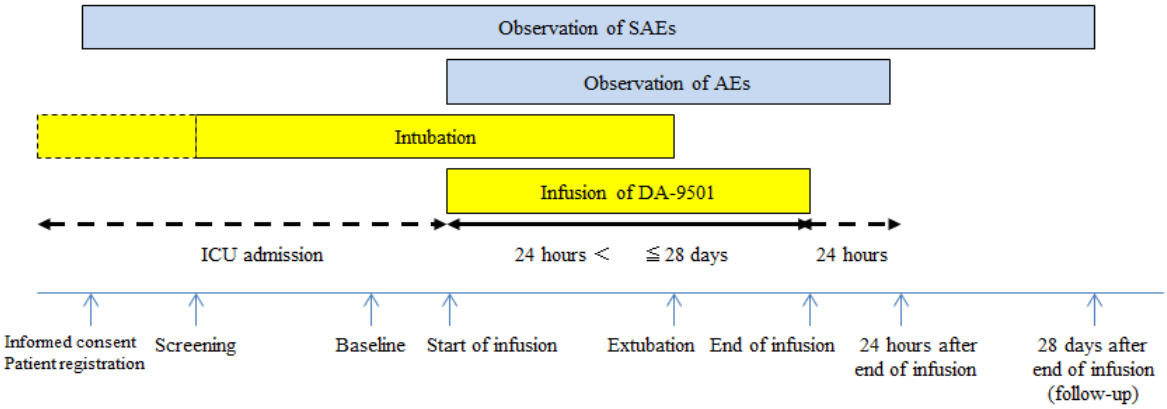
The schematic diagram of elective surgical subjects and medical ICU subjects are presented in Figure 1 and Figure 2, respectively. The schedule of study activities is presented in Table 1.

Figure 1. Elective Surgical Subjects



Abbreviations: AE=adverse events; ICU=intensive care unit; SAE=serious adverse event.

Figure 2. Medical ICU Subjects



Abbreviations: AE=adverse events; ICU=intensive care unit; SAE=serious adverse event.

Table 1. Schedule of Study Activities

Item	Screening (1 to 7 Days Before BL)[a]	Baseline (BL)[b]	From Start of Dosing to 24 Hours After Dosing or End of Mechanical Ventilation[c]	From 24 Hours After Dosing to End of Mechanical Ventilation[d]	From End of Mechanical Ventilation to End of Dosing of Study Drug[e]	24 Hours (±5 Minutes) After End of Dosing of Study Drug[f]	Follow-Up Period (28 Days After End of Dosing of Study Drug)
Informed consent[g]	X						
Subject registration	X						
Inclusion/exclusion criteria	X						
Subject demographics/medical history	X						
Surgery/actions, primary disease name etc	X	X					
Physical examination	X	X				X	
Height	X						
Body weight[h]	X	X				X	
Core body temperature[i]	X	X	→	→	→	X	
Vital signs (BP, HR, RR), SpO_2, $ETCO_2$[j]	X	X	→	→	→	X	
12-lead ECG	X	X[k]				X	
ECG monitoring		→	→	→	→	→	
Laboratory tests (hematology test, blood biochemistry tests, urinalysis)	X	X[l]	(X): To be performed as needed.			X	
Pregnancy test[m]	X						
Ventilator setting[n]			→	→			
Total input/output fluid volume					X		
Sedation assessment[o]		X	→	→	→	X	
Administration of study drug			→	→	→		
Rescue sedative assessment			→	→	→		
Rescue analgesic assessment			→	→	→		
Concomitant medications, non-drug treatment[p]	X	→	→	→	→	X	
Adverse events			→	→	→	X	
Serious adverse events		→	→	→	→	→	→

Abbreviations: BL=baseline; BP=blood pressure; ECG=electrocardiogram; $ETCO_2$=end tidal carbon dioxide; HR=heart rate; ICU=intensive care unit; RR=respiratory rate; SpO_2=oxygen saturation of arterial blood.

a. Heart rate (only measured by 12-lead ECG), 12-lead ECG, laboratory tests and pregnancy test that were measured in a general practice before obtaining the informed consent could be used as screening data. The data was measured within 7 days before screening.

b. In medical ICU subjects, the items for baseline was performed before dosing of the study drug on the start date of treatment with the study drug. In elective surgical subjects,

Table 1. Schedule of Study Activities

the items were performed after surgery (except body weight).

c. If mechanical ventilation management ended within 24 hours of dosing of the study drug.
d. If dosing of dexmedetomidine continued for 24 hours or longer and mechanical ventilation management was done.
e. If dexmedetomidine was continuously used after the end of mechanical ventilation management.
f. Physical examination, body weight, 12-lead ECG and laboratory tests were performed at 24 hours±30 minutes after end of dosing of the study drug.
g. Prior to the study, written consent was obtained from a guardian of the subject. For subjects 7 years and older, it was desirable that an informed assent was also obtained from the pediatric subject him/herself when possible.
h. The dose level of the study drug was calculated based on the baseline body weight.
i. Core body temperature was measured at screening, at baseline, and subsequently, every 12 hours (±5 minutes) during dosing of the study drug, at the end of dosing of the study drug, and at 24 hours (±5 minutes) after the end of dosing of the study drug.
j. Vital signs, SpO_2, and $ETCO_2$ were measured at screening, at baseline, at 10±2 minutes, 20±2 minutes, 30±2 minutes, 1 hour±5 minutes, 2 hours±5 minutes, 4 hours±5 minutes after dosing of the study drug, and every 4 hours±5 minutes later than 4 hours after the start of dosing. $ETCO_2$ did not have to be measured, if it could not be measured during non-intubation (screening, after extubation). These items were measured every 4 hours±5 minutes from Day 2 of treatment to extubation. If the study drug was continuously dosed after extubation, the items were measured every 4 hours±5 minutes until the end of dosing of the study drug. When extubation was done, the items were measured at 5±2 minutes before extubation, and 5±2 minutes, 15±2 minutes, 30±2 minutes, 1 hour±5 minutes, 2 hours ±5 minutes, 4 hours±5 minutes, and 12 hours±5 minutes after extubation. When dosing of the study drug ended, the items were measured at the end of dosing of the study drug (+5 minutes), at 1 hour±5 minutes, 2 hours±5 minutes, and 4 hours±5 minutes after the end of dosing of the study drug, and every 4 hours±5 minutes later than 4 hours after the end of dosing of the study drug. In addition, the items were measured at 5±2 minutes immediately before changing the infusion rate of the study drug, at 5±2 minutes after changing the rate, and at 5±2 minutes immediately before dosing of the rescue sedative (midazolam) and the rescue analgesic (fentanyl).
k. Baseline 12-lead ECG was performed only in elective surgical subjects. The item was performed after surgery. However, in subjects undergoing heart surgery, the item was performed after surgery and within 90 minutes before the start of dosing of the study drug.
l. Laboratory tests at baseline were performed only in elective surgical subjects. The item was performed after surgery. However, in subjects undergoing heart surgery, the item was performed after surgery and within 90 minutes before the start of dosing of the study drug.
m. Urinalysis or blood test was performed only in female subjects of childbearing potential.
n. If the mode of the ventilator was changed, the date/time of the change and the mode was recorded.
o. For sedation assessment, the level was measured at baseline, at 10±2 minutes, 20±2 minutes, 30±2 minutes, 1 hour±5 minutes, 2 hours±5 minutes, and 4 hours±5 minutes after dosing of the study drug, and every 4 hours±5 minutes later than 4 hours after the start of dosing. These levels were measured every 4 hours±5 minutes from Day 2 of treatment to extubation. If the study drug was continuously dosed after extubation, the levels were measured every 4 hours±5 minutes until the end of dosing of the study drug. When extubation was done, the levels were measured within 10 minutes before extubation, and 5±2 minutes, 15±2 minutes, 30±2 minutes, 1 hour±5 minutes, 2 hours±5 minutes, 4 hours±5 minutes, and 12 hours±5 minutes after extubation. When dosing of the study drug ended, the level was measured at the end of dosing of the study drug (+5 minutes), at 1 hour±5 minutes, 2 hours±5 minutes, and 4 hours±5 minutes after the end of dosing of the study drug, and every 4 hours±5 minutes later than 4 hours after the end of dosing of the study drug. In addition, the level was measured within 10 minutes immediately before changing the infusion rate of the study drug, at 3-30 minutes after changing the rate, and the level was measured within 10 minutes immediately before administration of the rescue sedative (midazolam) or rescue analgesic (fentanyl) and at 3-30 minutes after administration.
p. All concomitant medications from 48 hours before the start of dosing of the study drug to 24 hours after the end of dosing of the study drug was recorded. In addition, non-drug treatment from 48 hours before the start of dosing of the study drug to 24 hours after the end of dosing of the study drug was recorded.

Number of Subjects (Planned and Analyzed):

A total of 60 Subjects were planned to be enrolled in this study. The target number of subjects for efficacy/safety evaluation by age group are shown in Table 2.

Table 2. Target Number of Subjects

Age Group		Efficacy/Safety Evaluation: Target Number of Subjects
I	≥45 weeks CGA, <12 months	≥8
II	≥12 months, <24 months	≥16
III	≥2 years, <6 years	≥16
IV	≥6 years, <17 years	≥8
Target number of subjects		60

Abbreviation: CGA=corrected gestational age.

A total of 70 subjects were screened, of which 63 subjects were assigned and received study treatment.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Main Inclusion Criteria: Both male and female subjects with age of ≥45 weeks CGA to <17 years old at time of consent (consent was obtained in writing prior to the clinical study from a guardian after a full explanation) were included in the study. Female subjects of childbearing potential, were not pregnant or possibly pregnant, or lactating.

Elective surgical subjects: American Society of Anesthesiologists physical status classification of Class I to III by preoperative diagnosis; subjects who required at least 6 hours of respiratory management with intubation under intensive care from immediately after surgery. Medical ICU subjects: subjects who required at least 24 hours of respiratory management with intubation under intensive care were included in the study.

Main Exclusion Criteria: Subjects who were judged by investigator or sub-investigator to have a neurological disease that made sedation assessment difficult were excluded.

At the screening period, subjects with second or third degree heart block in the tests (excluding subjects using a pacemaker); with low blood pressure (BP) levels in the tests; with bradycardia; with alanine aminotransferase ≥100 U/L in the laboratory tests and with acute febrile illness were excluded. Subjects in whom dexmedetomidine or other α2 receptor agonists, α2 receptor antagonists and drug that could be used in this study were contraindicated were excluded.

Study Treatment:

A single vial containing an injection solution of 2 mL of dexmedetomidine hydrochloride solution (100 μg/mL as dexmedetomidine) dissolved in physiological saline, was provided by Sponsor. Study drug was prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance.

No initial loading dose was given. Baseline body weight was used to determine the dose of the study drug. Maintenance infusion was started at 0.2 µg/kg/h for all subjects. The infusion rate was adjusted within a range of 0.2 µg/kg/h to 1.4 µg/kg/h for ≥45 weeks CGA to <6 years old subjects and 0.2 µg/kg/h to 1.0 µg/kg/h for ≥6 years to <17 years old subjects according to the pediatric subject's sedative state.

Dosing Duration: Dosing of dexmedetomidine was started after the subject was admitted to the ICU. Dosing of dexmedetomidine could be continued after extubation as needed. The dosing duration was at least 6 hours in elective surgical subjects and at least 24 hours in medical ICU subjects for up to 28 days.

Target Sedation Depth: The target sedation depths during mechanical ventilation and after extubation were during mechanical ventilation (State Behavioral Scale [SBS] -2 to 0) and after extubation (SBS -1 to 0).

Efficacy Endpoints:

Primary Efficacy Endpoint:

The following item for the period from the start of dosing of the study drug to 24 hours of dosing or to the end of mechanical ventilation (when mechanical ventilation ended within 24 hours of dosing of the study drug):

1. Percentage of subjects who did not use a rescue sedative (midazolam) during mechanical ventilation to achieve/maintain adequate sedation (efficacy percentage).

Secondary Efficacy Endpoints:

The following items for the period from the start of dosing of the study drug to 24 hours of dosing or to the end of mechanical ventilation (when mechanical ventilation ended within 24 hours of dosing of the study drug):

1. Percentage of subjects who did not require administration of a rescue analgesic (fentanyl) during mechanical ventilation in addition to administration of the study drug.

2. Total amount and weight adjusted total amount of rescue sedative/analgesic during mechanical ventilation.

3. Absolute time and its percentage that subject was in the target sedation level during mechanical ventilation.

The following items for the period from 24 hours of dosing of the study drug to the end of mechanical ventilation in subjects whose period of dosing of the study drug exceeded 24 hours:

4. Percentage of subjects who did not use a rescue sedative during mechanical ventilation to achieve/maintain adequate sedation.

5. Percentage of subjects who did not require dosing of a rescue analgesic during mechanical ventilation in addition to dosing of the study drug.

6. Total amount and weight adjusted total amount of rescue sedative/analgesic during mechanical ventilation.

7. Absolute time and its percentage that subject was in the target sedation level during mechanical ventilation.

The following items for the period from extubation to the end of dosing of the study drug:

8. Absolute time and its percentage that subject was in the target sedation level after extubation.

9. Total amount and weight adjusted total amount of rescue sedative/analgesic.

The following item for the period from the start of dosing of the study drug to the end of mechanical ventilation:

10. Time until the end of mechanical ventilation.

Safety Evaluations:

Safety evaluations were laboratory tests, 12-lead electrocardiogram (ECG), vital signs (BP, heart rate, respiratory rate), percutaneous oxygen saturation, end-tidal carbon dioxide, core body temperature, body weight, total input/output fluid volume, adverse events (AEs), serious adverse events (SAEs) and withdrawal symptoms reporting. These were carried out at times specified in Table 1.

Statistical Methods:

Efficacy Analysis:

The full analysis set (FAS) was composed of all subjects who had received at least 1 dose of the study drug. The analysis population for efficacy evaluation was FAS.

Primary Efficacy Endpoint Analysis: The efficacy percentage of dexmedetomidine and its 95% confidence interval (CI) was calculated for all subjects in FAS, and the 95% lower confidence limit was compared to the threshold value (40%).

Secondary Efficacy Endpoint Analysis: The continuous variables were summarized by using basic statistics such as mean, median, standard deviation, quartiles and range. For categorical variables, the number of subjects and its percentage in each category were summarized. The analyses were performed for whole subjects as well as for each age group for all the 4 types of secondary endpoints (endpoints for responder [Secondary Endpoints 1, 4 and 5], endpoints for dosage [Secondary Endpoints 2, 6 and 9], endpoints for maintenance time of target sedation [Secondary Endpoints 3, 7 and 8] and endpoint of time to event [Secondary Endpoint 10]).

Safety Analysis:

The definition of safety analysis set is same as that of FAS. Safety evaluation was summarized based on "Pfizer data standards" and investigated clinically.

RESULTS

Subject Disposition and Demography:

The overall disposition of the subjects for the entire study is presented in Table 3. A total of 70 subjects were screened, of which 63 subjects were assigned and received study treatment (14 subjects aged ≥45 weeks CGA to <12 months; 18 subjects aged ≥12 months to <24 months; 19 subjects aged ≥2 years to <6 years and 12 subjects aged ≥6 years to <17 years). Two (2) male subjects discontinued from the study in the ≥2 years to <6 years age group.

Table 3. Subject Evaluation Groups - FAS

Number (%) of Subjects	≥45 Weeks CGA to <12 Months	≥12 Months to <24 Months	≥2 Years to <6 Years	≥6 Years to <17 Years	Total
Screened					70
Assigned to study treatment	14	18	19	12	63
Treated	14 (100.0)	18 (100.0)	19 (100.0)	12 (100.0)	63 (100.0)
Completed	14 (100.0)	18 (100.0)	17 (89.5)	12 (100.0)	61 (96.8)
Discontinued	0	0	2 (10.5)	0	2 (3.2)
Relation to study drug not defined	0	0	1 (5.3)	0	1 (1.6)
Other[a]	0	0	1 (5.3)	0	1 (1.6)
Not related to study drug	0	0	1 (5.3)	0	1 (1.6)
Adverse event	0	0	1 (5.3)	0	1 (1.6)
Analyzed for efficacy					
FAS	14 (100.0)	18 (100.0)	19 (100.0)	12 (100.0)	63 (100.0)
Analyzed for safety					
Adverse events	14 (100.0)	18 (100.0)	19 (100.0)	12 (100.0)	63 (100.0)
Laboratory data	14 (100.0)	18 (100.0)	18 (94.7)	12 (100.0)	62 (98.4)

Discontinuations were attributed to the last study treatment received.
Abbreviations: CGA=corrected gestation age; FAS=full analysis set.
a. Investigator's judgement.

Summary of subject types (evaluable, elective surgery and medical ICU for FAS is presented in Table 4.

Table 4. Summary of Subject Types - FAS

Number (%) of Subjects	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months	≥12 Months to <24 Months	≥2 Years to <6 Years	≥6 Years to <17 Years	Total
Evaluable subjects	14	18	19	12	63
Elective surgery	13 (92.9)	18 (100.0)	18 (94.7)	12 (100.0)	61 (96.8)
Medical ICU	1 (7.1)	0	1 (5.3)	0	2 (3.2)

Abbreviations: CGA=corrected gestation age; FAS=full analysis set; ICU=intensive care unit.

A summary of the demographic characteristics for FAS is presented in Table 5, with all of the subjects being Asian (Japanese).

Table 5. Demographic Characteristics - FAS

	≥45 Weeks CGA to <12 Months	≥12 Months to <24 Months	≥2 Years to <6 Years	≥6 Years to <17 Years	Total
Number (%) of Subjects	**14**	**18**	**19**	**12**	**63**
Gender					
Male	6 (42.9)	11 (61.1)	12 (63.2)	7 (58.3)	36 (57.1)
Female	8 (57.1)	7 (38.9)	7 (36.8)	5 (41.7)	27 (42.9)
Age					
≥45 W CGA to <12 M	14 (100.0)	0	0	0	14 (22.2)
≥12 M to <24 M	0	18 (100.0)	0	0	18 (28.6)
≥2 Y to <6 Y	0	0	19 (100.0)	0	19 (30.2)
≥6 Y to <17 Y	0	0	0	12 (100.0)	12 (19.0)
Mean (SD) (M)	6.1 (2.1)	16.9 (3.6)	45.7 (14.6)	112.1 (37.9)	41.3 (41.8)
Range (M)	1-9	12-23	24-69	73-175	1-175
Race					
Asian	14 (100.0)	18 (100.0)	19 (100.0)	12 (100.0)	63 (100.0)
Weight (kg)					
Mean (SD)	6.3 (1.1)	9.3 (1.5)	15.2 (3.0)	29.2 (14.5)	14.2 (10.3)
Range	4.5-8.3	6.4-12.0	10.1-20.2	16.1-70.8	4.5-70.8
Height (cm)					
Mean (SD)	65.3 (5.2)	77.4 (5.9)	98.7 (11.3)	129.6 (18.6)	91.1 (24.9)
Range	55.0-72.8	66.8-93.7	82.1-117.0	111.0-167.2	55.0-167.2

Abbreviations: CGA=corrected gestation age; FAS=full analysis set; M=month; SD=standard deviation W=week; Y=year.

Efficacy Results:

Primary Efficacy Results:

Percentage of Subjects Who Did Not Use Rescue Midazolam Within 24 Hours or Conclusion of Mechanical Ventilation:

The value of the lower limit of 95% CI (66.0%) was obviously higher than the criteria of judgment for efficacy (40%) and the value of the point estimate (77.8%) was also higher than the expected efficacy percentage (60%) for total subjects. In addition, the efficacy percentages by age group were also higher than the expected efficacy percentage (Table 6).

Table 6. Percentage of Subjects Who Did Not Use Rescue Midazolam Within 24 Hours or Conclusion of Mechanical Ventilation - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=14)	≥12 Months to <24 Months (N=18)	≥2 Years to <6 Years (N=19)	≥6 Years to <17 Years (N=12)	Total (N=63)
Number of subjects with no rescue midazolam	11	12	15	11	49
Percent of subjects with no rescue midazolam	78.6	66.7	78.9	91.7	77.8
95% CI[a]	51.7-93.2	43.6-83.9	56.1-92.0	62.5-100.0	66.0-86.4

Abbreviations: CGA=corrected gestation age; CI=confidence interval; FAS=full analysis set; N=number of subjects.
a. 95% CI was calculated as a 2-sided, 2.5% upper and lower intervals, based on Agresti-Coull's method.

Secondary Efficacy Results:

Period 1: Within 24 Hours or Conclusion of Mechanical Ventilation:

1. Percentage of Subjects Who Did Not Require Rescue Analgesic (Fentanyl): A total of 88.9% of subjects did not require rescue fentanyl in the FAS. There was only minimal difference among age groups of FAS (Table 7).

Table 7. Percentage of Subjects Who Did Not Require Rescue Fentanyl Within 24 Hours or Conclusion of Mechanical Ventilation - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=14)	≥12 Months to <24 Months (N=18)	≥2 Years to <6 Years (N=19)	≥6 Years to <17 Years (N=12)	Total (N=63)
Number of subjects with no rescue fentanyl	12	18	18	8	56
Percent of subjects with no rescue fentanyl	85.7	100.0	94.7	66.7	88.9
95% CI[a]	58.8-97.2	79.3-100.0	73.5-100.0	38.8-86.4	78.5-94.8

Abbreviations: CGA=corrected gestation age; CI=confidence interval; FAS=full analysis set; N=number of subjects.
a. 95% CI was calculated as a 2-sided, 2.5% upper and lower intervals, based on Agresti-Coull's method.

2. Total Amount and Weight Adjusted Total Amount of Rescue Sedative (Midazolam)/Analgesic (Fentanyl): A total of 14 subjects used rescue midazolam in FAS. The median (range) of weight adjusted dosage was 0.180 mg/kg (0.04 to 0.70 mg/kg) within the FAS subjects (Table 8). A total of 7 subjects used rescue fentanyl in FAS. The median (range) of weight adjusted dosage was 4.92 µg/kg (2.0 to 22.0 µg/kg) within the FAS subjects (Table 9).

Table 8. Summary of Total Amount of Rescue Midazolam Within 24 Hours or Conclusion of Mechanical Ventilation - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=14)	≥12 Months to <24 Months (N=18)	≥2 Years to <6 Years (N=19)	≥6 Years to <17 Years (N=12)	Total (N=63)
Rescued Subjects					
Total dosage (mg)					
Number of subjects	3	6	4	1	14
Median	0.670	3.231	2.550	1.960	1.878
Range (min-max)	0.18-1.80	1.05-5.18	1.00-3.78	1.96-1.96	0.18-5.18
Weight adjusted dosage (mg/kg)					
Number of subjects	3	6	4	1	14
Median	0.100	0.330	0.145	0.100	0.180
Range (min-max)	0.04-0.26	0.10-0.70	0.08-0.20	0.10-0.10	0.04-0.70

Abbreviations: CGA=corrected gestation age; FAS=full analysis set; max=maximum; min=minimum; N=number of subjects.

Table 9. Summary of Total Amount of Rescue Fentanyl Within 24 Hours or Conclusion of Mechanical Ventilation - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=14)	≥12 Months to <24 Months (N=18)	≥2 Years to <6 Years (N=19)	≥6 Years to <17 Years (N=12)	Total (N=63)
Rescued Subjects					
Total dosage (µg)					
Number of subjects	2	0	1	4	7
Median	91.70	-	97.50	79.54	89.96
Range (min-max)	36.0-147.4	-	97.5-97.5	68.0-99.9	36.0-147.4
Weight adjusted dosage (µg/kg)					
Number of subjects	2	0	1	4	7
Median	15.00	-	5.00	4.10	4.92
Range (min-max)	8.0-22.0	-	5.0-5.0	2.0-4.9	2.0-22.0

Abbreviations: CGA=corrected gestation age; FAS=full analysis set; max=maximum; min=minimum; N=number of subjects.

3. Absolute Time and its Percentage That Subject Was in the Target Sedation Level: A total of 95.2% of subjects were in the target sedation level within the analysis period. Median (range) duration when subjects were in the target sedation level was 3.00 hours (0.0 to 24.0 hours) for 5.90 hours (1.9 to 24.0 hours) of total observed time. The median percentage of maintenance of the target sedation level was 60.86% (Table 10).

Table 10. Summary of Maintenance Time of Target Sedation Level Within 24 Hours or Conclusion of Mechanical Ventilation - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=14)	≥12 Months to <24 Months (N=18)	≥2 Years to <6 Years (N=19)	≥6 Years to <17 Years (N=12)	Total (N=63)
Maintenance time (hours)					
N (%)[a]	13 (92.9)	17 (94.4)	19 (100.0)	11 (91.7)	60 (95.2)
Median	6.55	3.53	1.52	2.88	3.00
Range (min-max)	0.0-22.0	0.0-12.7	0.2-24.0	0.0-5.9	0.0-24.0
Total time (hours)					
Median	9.38	5.88	4.00	4.37	5.90
Range (min-max)	5.3-24.0	1.9-17.2	1.9-24.0	1.9-6.5	1.9-24.0
Maintenance percentage (%)					
Median	59.56	74.94	57.07	71.05	60.86
Range (min-max)	0.0-100.0	0.0-87.5	9.5-100.0	0.0-100.0	0.0-100.0

Target sedation level: -2 to 0 while intubated, -1 to 0 after extubation.
Abbreviations: CGA=corrected gestation age; FAS=full analysis set; max=maximum; min=minimum; N=number of subjects.
a. Number (percent) means number of subjects that spent any amount of time in State Behavioral Scale target range and its percentage while descriptive summaries were calculated as 0 hour for subjects who had never met the target sedation score at the analysis point for the evaluation period.

Period 2: Over 24 Hours to the End of Mechanical Ventilation:

4. Percentage of Subjects Who Did Not Use Rescue Sedative (Midazolam): All subjects who were dosed over 24 hours and ended mechanical ventilation after 24 hours of dosing did not use rescue midazolam during the analysis period (Table 11).

Table 11. Percentage of Subjects Who Did Not Use Rescue Midazolam Over 24 Hours - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=2)	≥12 Months to <24 Months (N=0)	≥2 Years to <6 Years (N=1)	≥6 Years to <17 Years (N=0)	Total (N=3)
N[a]	2	0	1	0	3
Number of subjects with no rescue midazolam	2	-	1	-	3
Percent of subjects with no rescue midazolam	100.0	-	100.0	-	100.0
95% CI[b]	29.0-100.0	-	16.7-100.0	-	38.3-100.0

Abbreviations: CGA=corrected gestation age; CI=confidence interval; FAS=full analysis set; N=number of subjects.
a. Means the number of subjects who stopped both administration and mechanical ventilation at the points of over 24 hours after initial administration.
b. 95% CI was calculated as a 2-sided, 2.5% upper and lower intervals, based on Agresti-Coull's method.

5. Percentage of Subjects Who Did Not Require Dosing of a Rescue Analgesic (Fentanyl): All subjects who were dosed over 24 hours and ended mechanical ventilation after 24 hours of dosing did not require rescue fentanyl during the analysis period (Table 12).

Table 12. Percentage of Subjects Who Did Not Require Rescue Fentanyl Over 24 Hours - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=2)	≥12 Months to <24 Months (N=0)	≥2 Years to <6 Years (N=1)	≥6 Years to <17 Years (N=0)	Total (N=3)
N[a]	2	0	1	0	3
Number of subjects with no rescue fentanyl	2	-	1	-	3
Percent of subjects with no rescue fentanyl	100.0	-	100.0	-	100.0
95% CI[b]	29.0-100.0	-	16.7-100.0	-	38.3-100.0

Abbreviations: CGA=corrected gestation age; CI=confidence interval; FAS=full analysis set; N=number of subjects.

a. Means the number of subjects who stopped both administration and mechanical ventilation at the points of over 24 hours after initial administration.

b. 95% CI was calculated as a 2-sided, 2.5% upper and lower intervals, based on Agresti-Coull's method.

6. Total Amount and Weight Adjusted Total Amount of Sedative (Midazolam)/Analgesic (Fentanyl): All subjects who were dosed over 24 hours and ended mechanical ventilation after 24 hours of dosing did not use rescue midazolam/fentanyl during the analysis period.

7. Absolute Time and its Percentage That Subject Was in the Target Sedation Level: A total of 100.0% of subjects were in the target sedation level within the analysis period. Median (range) duration which subjects were in the target sedation level was 0.92 hours (0.3 to 1.3 hours) for 0.92 hours (0.3 to 2.6 hours) of total observed time. The median percentage of maintenance of the target sedation level was 100.0% (Table 13).

Table 13. Summary of Maintenance Time of Target Sedation Level Over 24 Hours - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=2)	**≥12 Months to <24 Months (N=0)**	**≥2 Years to <6 Years (N=1)**	**≥6 Years to <17 Years (N=0)**	**Total (N=3)**
N[a]	2	0	1	0	3
Maintenance time (hours)[b]					
n (%)[b]	2 (100.0)	0	1 (100.0)	0	3 (100.0)
Median	0.81	-	0.92	-	0.92
Range	0.3-1.3	-	0.9-0.9	-	0.3-1.3
Total time (hours)					
Median	1.45	-	0.92	-	0.92
Range	0.3-2.6	-	0.9-0.9	-	0.3-2.6
Maintenance percentage (%)[b]					
Median	75.00	-	100.00	-	100.00
Range	50.0-100.0	-	100.0-100.0	-	50.0-100.0

Target sedation level: -2 to 0 while intubated, -1 to 0 after extubation.
Abbreviations: CGA=corrected gestation age; FAS=full analysis set; N=number of subjects; n=number of subjects for the specific category.

a. Means the number of subjects who stopped both administration and mechanical ventilation at the points of over 24 hours after initial administration.
b. Means number of subjects that spent any amount of time in State Behavioral Scale target range and its percentage while descriptive summaries were calculated as 0 hour for subjects who had never met the target sedation score at the analysis point for the evaluation period.

Period 3: From Extubation to the End of Dosing of the Study Drug:

8. Absolute Time and its Percentage That Subject Was in the Target Sedation Level: A total of 96.7% of subjects were in the target sedation level within the analysis period. Median (range) duration which subjects were in the target sedation level was 7.95 hours (0.0 to 43.3 hours) for 13.32 hours (0.5 to 60.7 hours) of total observed time. The median percentage of maintenance of the target sedation level was 57.11 (Table 14). Percentage of subjects who were in the target sedation level and summary statistics of the percentage of maintenance of the target sedation level were comparable to those within 24 hours or the end of mechanical ventilation (Table 10).

Table 14. Summary of Maintenance Time of Target Sedation Level After Extubation - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=14)	≥12 Months to <24 Months (N=18)	≥2 Years to <6 Years (N=16)	≥6 Years to <17 Years (N=12)	Total (N=60)
N	14	18	16	12	60
Maintenance time (hours)[a]					
n (%)[a]	14 (100.0)	18 (100.0)	16 (100.0)	10 (83.3)	58 (96.7)
Median	10.18	5.97	8.31	8.12	7.95
Range	0.1-43.3	0.2-33.6	0.5-14.9	0.0-13.6	0.0-43.3
Total time (hours)					
Median	12.77	13.47	14.10	12.67	13.32
Range	0.5-60.7	1.9-60.1	8.6-19.9	2.2-15.5	0.5-60.7
Maintenance percentage (%)[a]					
Median	72.67	52.23	50.43	62.30	57.11
Range	16.7-100.0	3.2-100.0	2.5-100.0	0.0-100.0	0.0-100.0

Target sedation level: -2 to 0 while intubated, -1 to 0 after extubation.
N means the number of subjects who stopped administration after extubation.
Subjects whose State Behavioral Scale scores did not be collected at the end of treatment were excluded from this summary.
Abbreviations: CGA=corrected gestation age; FAS=full analysis set; N=number of subjects; n=number of subjects for the specific category.

a. Means number of subjects that spent any amount of time in State Behavioral Scale target range and its percentage while descriptive summaries were calculated as 0 hour for subjects who had never met the target sedation score at the analysis point for the evaluation period.

9. Total Amount and Weight Adjusted Total Amount of Rescue Sedative (Midazolam)/Analgesic (Fentanyl): A total of 5 subjects used rescue midazolam. The median (range) of weight adjusted dosage was 0.093 mg/kg (0.04 to 0.37 mg/kg) within the FAS subjects (Table 15). Only 1 subject was given weight adjusted rescue fentanyl of 3.00 μg/kg.

Table 15. Summary of Total Amount of Rescue Midazolam After Extubation - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months (N=14)	≥12 Months to <24 Months (N=18)	≥2 Years to <6 Years (N=17)	≥6 Years to <17 Years (N=12)	Total (N=61)
Rescued Subjects					
Total dosage (mg)					
Number of subjects	2	2	1	0	5
Median	0.537	0.719	5.994	-	0.801
Range	0.27-0.80	0.48-0.96	5.99-5.99	-	0.27-5.99
Weight adjusted dosage (mg/kg)					
Number of subjects	2	2	1	0	5
Median	0.109	0.072	0.370	-	0.093
Range	0.04-0.18	0.05-0.09	0.37-0.37	-	0.04-0.37

Abbreviations: CGA=corrected gestation age; FAS=full analysis set; N=number of subjects.

Period 4: From the Start of Administration to the End of Mechanical Ventilation:

10. Time to Conclusion of Mechanical Ventilation From the Start of Dexmedetomidine Administration: Time to conclusion of mechanical ventilation from the start of dexmedetomidine administration is summarized in Table 16.

Table 16. Time to Conclusion of Mechanical Ventilation From the Start of Dexmedetomidine Administration - FAS

	Dexmedetomidine				
	≥45 Weeks CGA to <12 Months	≥12 Months to <24 Months	≥2 Years to <6 Years	≥6 Years to <17 Years	Total
Number of subjects evaluated	14	18	19	12	63
Subjects with conclusion of mechanical ventilation (%)	14 (100.0)	18 (100.0)	19 (100.0)	12 (100.0)	63 (100.0)
Censored (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Time to conclusion of mechanical ventilation (hours) Kaplan-Meier Estimates					
Percentiles (95% CI)					
25%	6.3 (6.0, 10.9)	4.1 (3.6, 6.0)	2.5 (2.3, 4.1)	3.3 (2.6, 4.8)	4.0 (3.6, 4.8)
50%	9.5 (6.3, 17.5)	6.0 (4.6, 6.3)	4.1 (3.0, 6.0)	4.5 (3.8, 6.0)	6.0 (4.8, 6.2)
75%	17.5 (8.0, 24.5)	7.0 (6.0, 16.2)	6.0 (4.1, 7.8)	6.1 (4.1, 6.5)	7.1 (6.2, 10.9)

Abbreviations: CGA=corrected gestation age; CI=confidence interval; FAS=full analysis set.

Safety Results:

Serious Adverse Events/Discontinuations due to Adverse Events:

One (1) SAE of moderate cardiac tamponade reported in ≥2 years to <6 years age group; considered not related to the treatment by the investigator; this subject was permanently discontinued from the study; no other subject permanently discontinued from the study due to treatment-emergent adverse events (TEAEs). There were no subjects with dose reductions or temporary discontinuations due to TEAEs during the study.

Non-Serious Adverse Events:

The incidence of all-causalities and treatment-related non-serious TEAEs (by system organ class and preferred term) are summarized in Table 17. All TEAEs were mild or moderate in severity.

Table 17. Incidence of Treatment-Emergent Adverse Events; All-Causalities and Treatment-Related

System Organ Class MedDRA Preferred Term	Dexmedetomidine														
	≥45 Weeks CGA to <12 Months			≥12 Months to <24 Months			≥2 Years to <6 Years			≥6 Years to <17 Years			Total		
	N[a] (%)	N1[b]	N2[c]	N[a] (%)	N1[b]	N2[c]	N[a] (%)	N1[b]	N2[c]	N[a] (%)	N1[b]	N2[c]	N[a] (%)	N1[b]	N2[c]
Evaluable for adverse events	14	-	-	18	-	-	19	-	-	12	-	-	63	-	-
With adverse events	11 (78.57)	-	-	16 (88.89)	-	-	16 (84.21)	-	-	12 (100.00)	-	-	55 (87.30)	-	-
Blood and lymphatic system disorders	0	0	0	1 (5.56)	1	0	1 (5.26)	1	0	0	0	0	2 (3.17)	2	0
Iron deficiency anaemia	0	0	0	1 (5.56)	1	0	1 (5.26)	1	0	0	0	0	2 (3.17)	2	0
Cardiac disorders	6 (42.86)	14	7	7 (38.89)	8	1	5 (26.32)	5	2	2 (16.67)	3	1	20 (31.75)	30	11
Bradycardia	6 (42.86)	14	7	7 (38.89)	8	1	5 (26.32)	5	2	2 (16.67)	3	1	20 (31.75)	30	11
Gastrointestinal disorders	1 (7.14)	1	1	2 (11.11)	2	0	4 (21.05)	7	1	7 (58.33)	12	3	14 (22.22)	22	5
Abdominal discomfort	0	0	0	0	0	0	1 (5.26)	1	0	0	0	0	1 (1.59)	1	0
Abdominal pain	0	0	0	0	0	0	0	0	0	1 (8.33)	1	0	1 (1.59)	1	0
Dry mouth	0	0	0	0	0	0	1 (5.26)	1	0	0	0	0	1 (1.59)	1	0
Gastric mucosal lesion	0	0	0	0	0	0	1 (5.26)	1	0	0	0	0	1 (1.59)	1	0
Mouth ulceration	0	0	0	1 (5.56)	1	0	0	0	0	0	0	0	1 (1.59)	1	0
Nausea	0	0	0	0	0	0	2 (10.53)	2	0	5 (41.67)	5	1	7 (11.11)	7	1
Vomiting	1 (7.14)	1	1	1 (5.56)	1	0	2 (10.53)	2	1	5 (41.67)	6	2	9 (14.29)	10	4
General disorders and administration site conditions	1 (7.14)	1	0	2 (11.11)	2	0	1 (5.26)	1	0	3 (25.00)	3	0	7 (11.11)	7	0
Injection site pain	0	0	0	0	0	0	0	0	0	1 (8.33)	1	0	1 (1.59)	1	0
Pyrexia	1 (7.14)	1	0	2 (11.11)	2	0	1 (5.26)	1	0	2 (16.67)	2	0	6 (9.52)	6	0
Infections and infestations	0	0	0	0	0	0	1 (5.26)	1	0	0	0	0	1 (1.59)	1	0
Pneumonia	0	0	0	0	0	0	1 (5.26)	1	0	0	0	0	1 (1.59)	1	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	1 (5.26)	1	0	0	0	0	1 (1.59)	1	0
Postoperative fever	0	0	0	0	0	0	1 (5.26)	1	0	0	0	0	1 (1.59)	1	0
Investigations	1 (7.14)	1	0	2 (11.11)	2	0	1 (5.26)	1	1	0	0	0	4 (6.35)	4	1
Body temperature increased	1 (7.14)	1	0	2 (11.11)	2	0	0	0	0	0	0	0	3 (4.76)	3	0
Electrocardiogram QT prolonged	0	0	0	0	0	0	1 (5.26)	1	1	0	0	0	1 (1.59)	1	1
Metabolism and nutrition disorders	0	0	0	0	0	0	1 (5.26)	1	1	0	0	0	1 (1.59)	1	1
Acidosis	0	0	0	0	0	0	1 (5.26)	1	1	0	0	0	1 (1.59)	1	1
Nervous system disorders	0	0	0	0	0	0	0	0	0	2 (16.67)	2	1	2 (3.17)	2	1
Headache	0	0	0	0	0	0	0	0	0	1 (8.33)	1	1	1 (1.59)	1	1
Neuralgia	0	0	0	0	0	0	0	0	0	1 (8.33)	1	0	1 (1.59)	1	0
Psychiatric disorders	4 (28.57)	10	3	2 (11.11)	4	0	1 (5.26)	1	0	0	0	0	7 (11.11)	15	3

Table 17. Incidence of Treatment-Emergent Adverse Events; All-Causalities and Treatment-Related

System Organ Class MedDRA Preferred Term	Dexmedetomidine														
	≥45 Weeks CGA to <12 Months			≥12 Months to <24 Months			≥2 Years to <6 Years			≥6 Years to <17 Years			Total		
	N[a] (%)	N1[b]	N2[c]	N[a] (%)	N1[b]	N2[c]	N[a] (%)	N1[b]	N2[c]	N[a] (%)	N1[b]	N2[c]	N[a] (%)	N1[b]	N2[c]
Agitation	4 (28.57)	10	3	2 (11.11)	4	0	1 (5.26)	1	0	0	0	0	7 (11.11)	15	3
Renal and urinary disorders	0	0	0	0	0	0	1 (5.26)	1	1	0	0	0	1 (1.59)	1	1
Acute kidney injury	0	0	0	0	0	0	1 (5.26)	1	1	0	0	0	1 (1.59)	1	1
Respiratory, thoracic and mediastinal disorders	4 (28.57)	6	0	8 (44.44)	20	0	4 (21.05)	7	0	6 (50.00)	24	2	22 (34.92)	57	2
Atelectasis	1 (7.14)	1	0	1 (5.56)	1	0	0	0	0	0	0	0	2 (3.17)	2	0
Hypoxia	1 (7.14)	1	0	0	0	0	0	0	0	0	0	0	1 (1.59)	1	0
Laryngeal oedema	0	0	0	1 (5.56)	1	0	0	0	0	0	0	0	1 (1.59)	1	0
Oropharyngeal pain	0	0	0	0	0	0	0	0	0	1 (8.33)	1	0	1 (1.59)	1	0
Pleural effusion	0	0	0	1 (5.56)	1	0	0	0	0	0	0	0	1 (1.59)	1	0
Respiratory depression	2 (14.29)	3	0	7 (38.89)	16	0	3 (15.79)	6	0	5 (41.67)	22	2	17 (26.98)	47	2
Respiratory disorder	0	0	0	0	0	0	0	0	0	1 (8.33)	1	0	1 (1.59)	1	0
Respiratory tract oedema	1 (7.14)	1	0	1 (5.56)	1	0	1 (5.26)	1	0	0	0	0	3 (4.76)	3	0
Skin and subcutaneous tissue disorders	1 (7.14)	1	0	1 (5.56)	1	0	0	0	0	0	0	0	2 (3.17)	2	0
Decubitus ulcer	0	0	0	1 (5.56)	1	0	0	0	0	0	0	0	1 (1.59)	1	0
Erythema	1 (7.14)	1	0	0	0	0	0	0	0	0	0	0	1 (1.59)	1	0
Vascular disorders	3 (21.43)	5	1	8 (44.44)	12	0	11 (57.89)	21	4	9 (75.00)	15	1	31 (49.21)	53	6
Hypertension	0	0	0	0	0	0	0	0	0	1 (8.33)	2	0	1 (1.59)	2	0
Hypotension	3 (21.43)	5	1	8 (44.44)	12	0	11 (57.89)	21	4	9 (75.00)	13	1	31 (49.21)	51	6

Except for 'N1' and 'N2' Subjects are only counted once per treatment for each row.
Percentages of gender specific events were calculated using the corresponding gender count as denominator.
Occurrences were calculated as the number of records having distinct value of subject identification number, start of adverse event, severity, causality and treatment group for that preferred term.
MedDRA (Version 20.0) coding dictionary applied.
Abbreviations: N=number of subjects; MedDRA=Medical Dictionary for Regulatory Activities.

a. The number of subjects in this reporting group affected by any occurrence of this adverse event, all-causalities.
b. The number of occurrences of treatment-emergent, all-causalities adverse events.
c. The number of occurrences of treatment-emergent, causally related to treatment adverse events.

Deaths:

There were no deaths reported during the study.

Clinical Laboratory Results:

No clinically significant changes were observed in laboratory parameters during the conduct of the study.

Vital Signs:

Systolic BP, diastolic BP and heart rate tended to decrease compared to baseline and no obvious changes were observed in the respiratory rate during dosing. Considering that only 4 subjects with treatment-emergent hypotension, bradycardia, and respiratory depression needed interventions (3 subjects with hypotension were given treatment and 1 subject with respiratory depression was given reduced dose of fentanyl); no clinically significant changes were observed in those vital signs data.

Electrocardiogram:

Overall, no clinically significant changes were observed in ECG data during the study.

CONCLUSIONS:

Efficacy percentage of dexmedetomidine, which was the primary analysis result of this study, was 77.8% (95% CI: 66.0-86.4). The lower limit of 95% CI was obviously higher than the criteria of judgment for efficacy (40%) and the point estimate was also higher than the expected efficacy percentage (60%). Therefore, based on predefined criteria for efficacy, the efficacy of dexmedetomidine was shown for pediatric subjects requiring sedation under intensive care. In addition, the efficacy percentages by age groups were also higher than the expected efficacy percentage.

There were no deaths, severe AEs, or dose reductions due to TEAEs reported in the study. One (1) subject permanently discontinued due to an SAE. The most common TEAEs were hypotension, bradycardia, and respiratory depression; majority of those causalities were ruled out. Only 4 subjects with most common TEAEs had interventions. No clinically significant changes were observed in laboratory parameters, ECG data and vital signs.