CLINICAL STUDY PROTOCOL

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

Compound:	DA-9501
Compound Name:	Dexmedetomidine hydrochloride
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	N/A
Protocol Number:	C0801017
Phase:	Phase 3

This protocol (English translation version, 21-Dec-2016) is intended to assist understanding of the original version of the protocol (Japanese version, 24-Mar-2016), and all implementation procedures and judgment standards should be in accordance with the descriptions in the original version.

[redacted]

Pfizer Japan Inc.
Maruishi Pharmaceutical Co., Ltd.

[redacted]

Document History

Document	Version Date	Summary of Changes
Amendment 2	24-Mar-2016	• Primary analysis population for efficacy endpoints was changed from efficacy evaluation population to full analysis set. • Data collection of non-drug treatment was added.
Amendment 1	10-Feb-2016	• The clinical study protocol template was changed from the Hospira version to the Pfizer version. • Laboratory tests were all changed to in-hospital tests. • Other administrative changes were made.
Original protocol	27-Jan-2016	Not applicable (N/A)

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PROTOCOL SUMMARY

Study Objectives: To evaluate the efficacy, safety, and pharmacokinetics (PK) of DA-9501 (dexmedetomidine hydrochloride; hereinafter referred to as "dexmedetomidine") administered as continuous intravenous injection (IV) infusion in pediatric subjects (≥45 weeks CGA [corrected gestational age] to <17 years old) who require sedation in the intensive care unit.

Study Design: Phase 3, multi-center, single-arm, open-label study evaluating the efficacy, safety, and PK of dexmedetomidine administered as continuous IV infusion in pediatric subjects aged ≥45 weeks CGA to <17 years old

Study Patients: Target number of subjects: 60 subjects

Of these subjects, at least 32 subjects aged ≥45 weeks CGA to <17 years old will be included in the PK evaluation. The target numbers of subjects included in the efficacy/safety evaluation and in the PK evaluation by age group are shown in the table below.

Age group		Efficacy/safety evaluation: Target number of subjects	PK evaluation: Target number of subjects*
I	≥45 weeks CGA,<12 months	≥8	≥8
II	≥12 months, <24 months	≥16	≥8
III	≥2 years, <6 years	≥16	≥8
IV	≥6 years, <17 years	≥8	≥8
Target number of subjects		60	≥32

* Of enrolled subjects, those from whom informed consent for blood sampling for PK evaluation is obtained

Investigational Product and Dosage/Administration:

Investigational product: DA-9501 (dexmedetomidine hydrochloride)

Dosage/administration:

≥45 weeks CGA to <6 years old: Start maintenance administration at 0.2 μg/kg/h. The infusion rate will be adjusted within a range of 0.2 to 1.4 μg/kg/h according to the pediatric subject's sedative state.

≥6 years to <17 years old: Start maintenance administration at 0.2 μg/kg/h. The infusion rate will be adjusted within a range of 0.2 to 1.0 μg/kg/h according to the pediatric subject's sedative state.

<Target Sedation Depth>

During mechanical ventilation: SBS −2 to 0; After extubation: SBS −1 to 0

Duration of Treatment with Investigational Product: The duration of treatment will be up to 28 days.

Efficacy Endpoints:

- Primary Efficacy Endpoint:

  The following item for the period from the start of dosing of the investigational product to 24 hours of dosing or to the end of mechanical ventilation (when mechanical ventilation ends within 24 hours of dosing of the investigational product):

  - 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 item for the period from the start of dosing of the investigational product to 24 hours of dosing or to the end of mechanical ventilation (when mechanical ventilation ends within 24 hours of dosing of the investigational product):

  - Percentage of subjects who did not require administration of a rescue analgesic (fentanyl)

during mechanical ventilation in addition to administration of the investigational product

- Total amount and weight adjusted total amount of rescue sedative/analgesic during mechanical ventilation
- 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 investigational product to the end of mechanical ventilation (in subjects whose period of dosing of the investigational product exceeds 24 hours):

- Percentage of subjects who did not use a rescue sedative during mechanical ventilation to maintain/achieve adequate sedation
- Percentage of subjects who did not require dosing of a rescue analgesic during mechanical ventilation in addition to dosing of the investigational product
- Total amount and weight adjusted total amount of rescue sedative/analgesic during mechanical ventilation
- 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 investigational product:

- Absolute time and its percentage that subject was in the target sedation level after extubation
- Total amount of rescue sedative/analgesic

The following item for the period from the start of dosing of the investigational product to the end of mechanical ventilation:

- Time until the end of mechanical ventilation

The evaluation will be performed by age group in addition to all subjects.

Safety Endpoints:

- Adverse events
- Vital signs (blood pressure, heart rate, respiratory rate), SpO_2, $ETCO_2$, core body temperature, and body weight
- Laboratory test values
- Total Input/Output Fluid Volume
- Occurrence of withdrawal symptoms (presence/absence of hypertension, tachycardia, or agitation symptoms after the end of dosing of the investigational product)
- Electrocardiogram (ECG)

The evaluation will be performed by age group in addition to all subjects.

CCI [redacted]

Statistical Methods:

Analysis for Primary Efficacy Endpoints:

Efficacy percentage of dexmedetomidine (percentage of subjects who did not use a rescue sedative (midazolam) during mechanical ventilation to achieve/maintain adequate sedation) and its 95% confidence interval will be calculated, and the 95% lower confidence limit will be compared to the threshold value (40%). Primary efficacy analysis will be performed for full analysis set. As secondary analysis, a similar analysis will be performed for the efficacy evaluation population. Efficacy percentages will be calculated by age group as well..

Analysis for Secondary Efficacy Endpoints:

Continuous variables will be summarized by using basic statistics such as mean, median, standard deviation and range. For categorical variables, the number of subjects and its percentage will be summarized. The analyses will be performed for whole subjects as well as for age groups.

Analysis for Safety Endpoints:

Safety evaluation will be performed for items such as changes from baseline. Also, the evaluation will be summarized based on "Pfizer Data Standards (PDS)" and investigated clinically. The analyses will be performed for whole subjects as well as for age groups.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1. Schedule of Study Activities

Item	Screening (1 to 7 days before BL)	Baseline (BL)*	From start of dosing to 24 hours after dosing or end of mechanical ventilation**	From 24 hours after dosing to end of mechanical ventilation***	From end of mechanical ventilation to end of dosing of investigational product****	24 hours (±5 min) after end of dosing of investigational product	Follow-up period (28 days after end of dosing of investigational product)
Informed consent[1]	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[2]	X	X				X	
Core body temperature[3]	X	X	→	→	→	X	
Vital signs (BP, HR, RR), SpO_2, $ETCO_2$[4]	X	X	→	→	→	X	
12-lead ECG	X	X[5]				X	
ECG monitoring		→	→	→	→	→	
Laboratory tests (hematology test, blood biochemistry tests, urinalysis)	X	X[6]	(X): To be performed as needed.			X	
Pregnancy test[7]	X						
Ventilator setting[8]			→	→			
Total input/output fluid volume					X		
Sedation assessment[9]		X	→	→	→	X	
Administration of investigational product			→	→	→		
Rescue sedative assessment			→	→	→		
Rescue analgesic assessment			→	→	→		
Concomitant medications, Non-drug treatment[10]	X	→	→	→	→	X	
Adverse events			→	→	→	X	
Serious adverse events		→	→	→	→	→	→

Item	Screening (1 to 7 days before BL)	Baseline (BL)*	From start of dosing to 24 hours after dosing or end of mechanical ventilation**	From 24 hours after dosing to end of mechanical ventilation***	From end of mechanical ventilation to end of dosing of investigational product****	24 hours (±5 min) after end of dosing of investigational product	Follow-up period (28 days after end of dosing of investigational product)
Blood sampling for plasma drug concentration[11]			→	→	→	→	

*: In medical ICU subjects, the items for baseline will be performed before dosing of the investigational product on the start date of treatment with the investigational product. In elective surgical subjects, the items will be performed after surgery.
**: If mechanical ventilation management ended within 24 hours of dosing of the investigational product.
***: If dosing of dexmedetomidine continued for 24 hours or longer and mechanical ventilation management was done.
****: If dexmedetomidine was continuously used after the end of mechanical ventilation management.

1. Prior to the study, written consent will be obtained from a guardian of the subject. For subjects 7 years and older, it is desirable that an informed assent is also obtained from the pediatric subject him/herself when possible.
2. The dose level of the investigational product will be calculated based on the baseline body weight.
3. Core body temperature will be measured at screening, at baseline, and subsequently, every 12 hours (±5 min) during dosing of the investigational product, at the end of dosing of the investigational product, and at 24 hours (±5 min) after the end of dosing of the investigational product.
4. Vital signs, SpO_2, and $ETCO_2$ will be 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 investigational product, and every 4 hours±5 minutes later than 4 hours after the start of dosing. These items will be measured every 4 hours±5 minutes from Day 2 of treatment to extubation. If the investigational product is continuously dosed after extubation, the items will be measured every 4 hours±5 minutes until the end of dosing of the investigational product. When extubation is done, the items will be 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 investigational product ends, the items will be measured at the end of dosing of the investigational product (+5 min), at 1 hour ± 5 minutes, 2 hours±5 minutes, and 4 hours±5 minutes after the end of dosing of the investigational product, and every 4 hours±5 minutes later than 4 hours after the end of dosing of the investigational product. In addition, the items will be measured at 5±2 minutes immediately before changing the infusion rate of the investigational product, at 5±2 minutes after changing the rate, and at 5±2 minutes immediately before and after dosing of the rescue sedative (midazolam) and the rescue analgesic (fentanyl).
5. Baseline 12-lead ECG will be performed only in elective surgical subjects. The item should be performed after surgery. However, in subjects undergoing heart surgery, the item should be performed after surgery and within 90 minutes before the start of dosing of the investigational product.
6. Laboratory tests at baseline will be performed only in elective surgical subjects. The item should be performed after surgery. However, in subjects undergoing heart surgery, the item should be performed after surgery and within 90 minutes before the start of dosing of the investigational product.
7. Urinalysis or blood test will be performed only in female subjects of childbearing potential.
8. If the mode of the ventilator was changed, the date/time of the change and the mode will be recorded.
9. For sedation assessment, the level will be 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 investigational product, and every 4 hours±5 minutes later than 4 hours after the start of dosing. These levels will be measured every 4 hours±5 minutes from Day 2 of treatment to extubation. If the investigational product is continuously dosed after extubation, the levels will be measured every 4 hours± 5 minutes until the end of dosing of the investigational product. When extubation is done, the levels will be 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 investigational product ends, the level will be measured at the end of dosing of the investigational product (+5 min), at 1 hour±5 minutes, 2 hours±5 minutes, and 4 hours±5 minutes after the end of dosing of the investigational product, and every 4 hours±5 minutes later than 4 hours after the end of dosing of the investigational product. In addition, the level will be measured at 5±2 minutes immediately before changing the infusion rate of the investigational product, at 5±2 minutes after changing the rate, and the level will be measured at 5±2 minutes immediately before administration of the rescue sedative (midazolam) or rescue analgesic (fentanyl) and at 5±2 minutes after administration.
10. All concomitant medications from 48 hours before the start of dosing of the investigational product to 24 hours after the end of dosing of the investigational product will be recorded. In addition, non-drug treatment from 48 hours before the start of dosing of the investigational product to 24 hours after the end of dosing of the investigational product will be recorded.

11. Blood sampling for plasma drug concentration will be performed 1-2 hours before the end of dosing of the investigational product, immediately before the end of dosing of the investigational product, and at 10 minutes, 30 minutes, 2 hours, 4 hours, and 6-8 hours after the end of dosing of the investigational product. When the dose of dexmedetomidine is tapered, blood sampling will be performed immediately before the start of tapering, immediately before the end of tapering, and at 10 minutes, 30 minutes, 2 hours, 4 hours, and 6-8 hours after the end of tapering.

List of Abbreviations

The following is a list of abbreviations used in the protocol.

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ASA	American Society of Anesthesiologists
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from time zero to infinity
AUC_{last}	area under the concentration-time curve from zero to time of last measurable concentration
CL	clearance
CL_w	weight adjusted clearance
C_{max}	maximum observed concentration
CRF	case report form
CSA	clinical study agreement
DMC	data monitoring committee
EC	ethics committee
ECG	electrocardiogram
EDP	exposure during pregnancy
$ETCO_2$	end-tidal CO_2
ETT	endotracheal tube
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ICU	intensive care unit
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IUD	intrauterine device
LFT	liver function test
N/A	not applicable
PCD	primary completion date
PD	pharmacodynamics
PK	pharmacokinetic(s)
PT	prothrombin time
SAE	serious adverse event
SBS	State Behavioral Scale
SC	subcutaneous
SIB	suicidal ideation and behavior

Abbreviation	Term
SOP	standard operating procedure
SpO_2	percutaneous oxygen saturation
SRSD	single reference safety document
$t_{½}$	elimination half-life
UMSS	University of Michigan Sedation Scale
US	United States
USPI	United States package insert
V_{ss}	steady-state volume of distribution
$V_{ss,w}$	weight adjusted steady-state volume of distribution
V_d	volume of distribution

1. INTRODUCTION

1.1. Mechanism of Action/Indication

DA-9501 (dexmedetomidine hydrochloride; hereinafter referred to as "dexmedetomidine") is a potent and highly selective central α2 adrenergic receptor agonist. It is currently under development as a sedative for pediatric patients under intensive care.

1.2. Background

Dexmedetomidine, which is the active ingredient of this drug, is an active dextro rotatory form (D form) of medetomidine with an imidazole skeleton. It was discovered by the Farmos Group in 1986. Dexmedetomidine is a potent and highly selective central α2 adrenergic receptor agonist. In addition to the sedative action, the drug is known to show a wide range of pharmacological actions, including inhibitory action on pain or anxiety and stabilizing action on the circulatory dynamics through alleviation of stress-induced hyperactivity of the sympathetic nervous system.[1, 2, 3]. Also, research conducted after that time indicated that the dosing of this drug could result in near natural sleep[4, 5] that it would be possible to ensure recovery of the consciousness level as necessary even when sufficient sedation was achieved through continuous infusion of this drug, and that it would be possible to maintain a state free of anxiety and pain.[5, 6]

Ideally, sedative drugs used in intensive care should show "good quality of sedation", "mild respiratory/circulatory inhibition", "easy adjustment of the sedation level and the ability to awaken the patient in a short period of time following the discontinuation of dosing", and "the ability to maintain analgesic activity at the same time". [5 7, 8, 9, 10, 11]

This drug shows almost none of the respiratory depression that is an issue with conventional sedatives,[12, 13, 14] and it was first approved in the United States (US) in December 1999 for "Sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Administer Precedex by continuous infusion not to exceed 24 hours mechanical ventilation" as a sedative that can be administered continuously not only during mechanical ventilation, but even after disconnection of the mechanical ventilation.[15] In Japan, a bridging study was started in March 2000 in order to investigate the "possibility of extrapolating foreign clinical data to Japanese patients", and the drug was first approved in January 2004 for "sedation during mechanical ventilation and following extubation in patients capable of early extubation and managed in the intensive care unit (ICU)".

However, in actual clinical settings, there are many patients requiring sedation for more than 24 hours while in the ICU, and in order to address the need for continuous dosing exceeding 24 hours in intensive care in Japan, a long-term dosing study (phase 3 study) was started in October 2007 with the objective of expanding the indications to sedation in intensive care exceeding 24 hours. As a result, the safety and efficacy of this drug during long term dosing were confirmed, leading to approval of the drug in August 2010 for "Sedation during and after mechanical ventilation in the intensive care setting".

No particular issues were observed in terms of efficacy or safety in the post marketing surveillance, and the reexamination results on March 24, 2014 indicated that "none of the matters listed in Article 14, Paragraph 2, Item 3 of the Pharmaceuticals and Medical Devices Law (reasons for denial of approval) were applicable".

Also, this drug causes milder respiratory depression compared with other sedatives[16, 17, 18] and communication is possible with the patient under appropriate depth of sedation.[7, 16, 17] Because of these characteristics, requests started to emerge from medical settings to use this drug in sedation during surgery or other procedures without intubation and with a local anesthetic. In the US, the drug has already been approved in 2008 for the indication of use in sedation during surgery and procedures without intubation under local anesthesia. In order to obtain approval for this indication in Japan, a study targeting subjects undergoing surgery or procedures without intubation under local anesthesia such as local infiltration or conduction anesthesia as well as a study on subjects undergoing surgery without intubation under epidural or spinal subarachnoid anesthesia were started in 2011 (each study was a phase 3, randomized, placebo-controlled, double-blind comparative study). As a result, the efficacy and safety of this drug were confirmed, leading to the approval of the drug in June 2013 for "sedation of non-intubated patients at surgical or other procedures under local anesthesia".

This drug is used in clinical practice to treat children as well, and the use of this drug as a sedative is described in guidelines such as the "Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases" [18] and the "Guidelines for the use of Anesthesia and Anesthesia-related Drugs". [19] Further, there was a request for pediatric indications for this drug from academic societies at the start of the "Council for Paediatric Pharmacotherapy"[20], and in consideration of these academic society requests as well as current medical practice in Japan, the study is planned to obtain approval of pediatric indication in Japan.

Dexmedetomidine has been approved as a sedative in intensive care treatment of adults in 70 countries across the world, and it has been approved for use as a sedative during surgery or procedures without intubation under local anesthesia in 26 countries. No approval for use of this drug in children has been obtained in any country.

1.3. Non-Clinical Studies

Prior to the conduct of a study in children, the following non-clinical studies in juvenile animals were conducted.

Dexmedetomidine was subcutaneously administered to adult and juvenile rats to determine the effect of age on the plasma concentration of dexmedetomidine. Dexmedetomidine was rapidly absorbed and eliminated. Differences in the maximum observed concentration (C_{max}) and elimination half-life ($t_{½}$) between two age groups were expected due to the metabolism rate. C_{max} values in adult and juvenile rats were 23.81±6.05 ng/mL and 10.79±0.99 ng/mL, respectively, and the area under the concentration-time curve (AUC) values were 53.5 ng·h/mL and 19.9 ng·h/mL, respectively. Plasma clearance (CL) values were 1.9 L/h·kg and 5.0 L/h·kg, respectively.

Dexmedetomidine was rapidly eliminated following intravenously administration to adult and juvenile dogs. Differences in $t_{½}$ were expected due to the metabolism rate in the 2 age groups. AUCs were 118.0±37.4 ng·h/mL and 36.6± 2.2 ng·h/mL for adult and juvenile dogs, respectively, and plasma CLs were 0.4±0.1 L/h·kg and 1.2±0.1 L/h·kg, respectively.

A repeated-dose toxicity study in juvenile beagle dogs was conducted to investigate the potential effects of dexmedetomidine on juvenile animals and to determine if effects were produced in juvenile dogs that were not found in adults. Administration of 15, 25, or 50 μg/kg/day dexmedetomidine over a 6-hour infusion period daily for 2 weeks was well tolerated by juvenile beagle dogs. Extending the dosing period to a 6-hour infusion had no effect on the tolerability or toxicity of dexmedetomidine, and these findings concur with those of the study in adult dogs, in which dexmedetomidine was intravenously administered as a bolus each day for 28-day. The finding of increased bile acids in individual dogs receiving 15 or 25 μg/kg/day dexmedetomidine was not considered as toxicological significant, since there was no histopathologic evidence of hepatotoxicity, and none of the dogs in the 50 μg/kg/day group had increased bile acids.

In a neurotoxicity study in juvenile rats, dexmedetomidine administrations, at 3, 10, or 30 μg/kg, did not produce any increase in neurodegeneration, and the numbers of degenerating cells were equivalent to saline.

Regarding other non-clinical study data, see the Investigator's Brochure.

1.4. Clinical Studies (from the Investigator's Brochure)

Overseas, phase 1 studies [Study W98-266 and Study CHOP] and 5 phase 2 or 3 studies [Studies DEX-08-01, DEX-11-01, DEX-09-08, DEX-11-06, and DEX-08-05] in pediatric subjects under intensive care have been completed.

A summary of a pharmacokinetic (PK) study is described below. A phase 1, multi-center, open-label study to evaluate the PK and pharmacodynamics (PD) of dexmedetomidine when administered as a single dose preoperatively to 36 pediatric subjects aged 2 to 12 years was conducted (Study W98-266). As loading doses, dexmedetomidine was intravenously infused at 0.33 μg/kg, 0.66 μg/kg, and 1 μg/kg over 10 minutes. In adults, the mean body weight adjusted clearance (CL_w) and mean volume of distribution (V_d) for dexmedetomidine were 0.53 L/h/kg and 1.31 L/kg, respectively, but the mean CL_w and the mean volume of distribution at steady state (V_{ss}) in children in this study were 0.848 L/h/kg and 1.65 L/kg, respectively. Plasma protein binding ratio in the pediatric population was comparable to that in adults. The ratios were 92.64% and 93.72%, respectively. All of the children treated with dexmedetomidine became drowsy or sedated, and well tolerated to dexmedetomidine. Between the start of treatment and the start of surgery, adverse events (AEs) were observed in three subjects: hypertension in 1 subject and oxygen saturation <95% in 2 subjects.

A phase 2, open-label, multi-center, dose-escalation pediatric study (Study DEX-08-01) to clarify the PK and PD profiles of dexmedetomidine was conducted in 2 age groups: ≥2 years to <6 years old (26 subjects) and ≥6 years to <17 years old (33 subjects). Within each age group,

the following 4 escalating dose levels were set up: 0.25 μg/kg loading dose, 0.2 μg/kg/h maintenance dose (Dose 1); 0.5 μg/kg loading dose, 0.4 μg/kg/h maintenance dose (Dose 2); 1 μg/kg loading dose, 0.7 μg/kg/h maintenance dose (Dose 3); and 1 μg/kg loading dose, 2 μg/kg/h maintenance dose (Dose 4). A loading dose of the investigational product was to be given over 10 minutes, and a maintenance dose was to be given over 6 to 24 hours. The PK profile demonstrated linearity and dose-proportionality among the Dose 1, Dose 2, Dose 3, and Dose 4 groups. The AUC and C_{max} increased in proportion to increasing dose. The $t_{½}$ in the Dose 1, Dose 2, Dose 3, and Dose 4 groups were 1.546 hours, 1.743 hours, 2.045 hours, and 2.145 hours, respectively. The overall level of sedation was higher in the Dose 4 group in subjects aged ≥6 to <17 years old compared to other treatment groups. The most frequently occurring AEs in both age groups were hypokalemia, pyrexia, vomiting, and hypertension. One subject experienced a serious adverse event (SAE), but the event was judged to be "Unrelated" to the investigational product. The 4 dose levels of dexmedetomidine studied were generally well-tolerated, and there were no clinically meaningful differences observed among dose levels in the safety profile of dexmedetomidine.

In a phase 2, randomized, open-label, single-center study (Study DEX-11-01), the PK, PD, and safety of dexmedetomidine were evaluated in intubated and mechanically ventilated pediatric subjects aged 12 months to <24 months by using 2 doses of dexmedetomidine (a loading dose of 0.7 μg/kg immediately followed by a maintenance dose of 0.5 μg/kg/h and a loading dose of 1 μg/kg immediately followed by a maintenance dose of 0.75 μg/kg/h). A loading dose was to be given over 10 minutes and a maintenance dose was to be given over 6 to 24 hours. The exposure to dexmedetomidine (C_{max} and AUC) was considered to be related to the dose, whereas the $t_{½}$, CL, and V_d were not dependent of the dose. Observed time to reach maximum plasma concentration (T_{max}) was generally 0.08 hours before the end of the loading dose, and was fairly consistent across all subjects and dose groups. The maintenance doses of dexmedetomidine used in this study were moderately effective for sedating and keeping subjects comfortable. Compared to Dose level 2 subjects, Dose level 1 subjects spent considerably less time in the target University of Michigan Sedation Scale (UMSS) range of 2 to 4, but had lower total Faces, Legs, Activity, Cry and Consolability (FLACC) scores. Dexmedetomidine was safe and well tolerated at both dose levels. One of the 5 enrolled subjects experienced mild AEs of pyrexia and atelectasis, but both were assessed as "Unrelated" to dexmedetomidine.

In a Phase 2/3 open-label, multicenter, safety, efficacy and PK study, dexmedetomidine were administered as an intravenous injection (IV) loading dose followed by a continuous IV infusion, in initially intubated and mechanically ventilated neonates ages ≥28 weeks to ≤44 weeks gestational age (GA), in a neonatal, cardiac, or pediatric intensive care unit (CICU or PICU) (Study DEX-09-08). Subjects were divided into 2 age groups (premature neonates ≥28 weeks to <36 weeks GA and term neonates ≥36 weeks to ≤44 weeks GA). Within each group, there were 3 escalating dose levels (consisting of a loading dose immediately followed by a maintenance dose up to 24 hours). The results of the PK analysis suggested that the body weight adjusted volume of distribution at steady state ($V_{ss,w}$) and $t_{½}$ were comparable across dose levels and age groups. In addition, the exposure of dexmedetomidine appeared to be dose-proportional in preterm neonates and term neonates. Dose-proportionality in younger

subjects could not be assessed. Premature neonates appeared to have lower CL_w compared to term neonates, which resulted in higher exposure adjusted for dose. The lower CL and higher concentrations in this age group were consistent with the greater efficacy observed in the premature neonates (no subjects required rescue administration of midazolam for sedation and 1 subject required rescue administration of a medication for analgesia) compared to the term neonates (4 subjects required rescue administration of midazolam for sedation and 14 subjects required rescue administration of a medication for analgesia). Dexmedetomidine was safe and well tolerated in both age groups and at all dose levels used in the study. Three subjects experienced 4 AEs assessed as related to treatment, namely diastolic hypotension, respiratory acidosis, hypertension, and anger.

In a phase 2/3 open-label, multicenter, safety and efficacy study, dexmedetomidine were administered as an IV loading dose followed by a continuous IV infusion in initially intubated and mechanically ventilated preterm subjects, ≥28 weeks through <36 weeks, GA, having a weight of >1000 g, in an intensive care setting anticipated to require at least 6 hours of continuous IV sedation (Study DEX-11-06). All of the 6 enrolled subjects received dexmedetomidine at 0.2 μg/kg as a loading dose over 10 or 20 minutes followed by continuous maintenance infusion of dexmedetomidine at a rate of 0.2 μg/kg/h over 6 to 24 hours. The efficacy evaluation was performed by assessing the sedation level with the use of the Neonatal Pain, Agitation, and Sedation Scale (N-PASS) developed to assess sedation and pain/agitation in neonates. From the results of the study, it was concluded that dexmedetomidine at the doses used in the study was an effective sedative and was safe and well tolerated in premature neonates aged ≥28 weeks to <36 weeks GA who were mechanically ventilated with intubation at the start of treatment. Most premature neonates (5 out of 6) did not require additional medication for pain while on dexmedetomidine infusion. One subject received rescue administration of a medication for analgesia during infusion of the investigational product. Subjects spent a short period of time with a total N-PASS score >3, indicating that most subjects were adequately sedated and did not manifest signs of pain/agitation. There were no deaths, SAEs, AEs leading to dexmedetomidine discontinuation, or dose-limiting toxicities that led to dexmedetomidine discontinuation.

In a phase 3, randomized, double-blind, dose-comparative, multi-center study (Study DEX-08-05), the safety and efficacy of dexmedetomidine were evaluated in pediatric ICU subjects aged 1 month to <17 years who were mechanically ventilated with intubation. Enrolled subjects were randomized to receive either high dose or low dose of dexmedetomidine and were stratified according to the presence or absence of cardiopulmonary bypass (CPB). Dexmedetomidine was effective for sedating critically ill infants and children who were mechanically ventilated with intubation at the start of treatment, following major cardiac surgery with CPB or noncardiac surgery. Although not significant, a dose-response effect was observed in the high dose group (54.3%), with more subjects who did not require rescue administration of midazolam to maintain the target sedation level than in the low dose group (44.6%). High dose dexmedetomidine showed the highest level of efficacy in subjects who underwent cardiac surgery, with more subjects who did not require rescue administration of midazolam for sedation. Dexmedetomidine was well tolerated at all doses used in the study in both cardiac and noncardiac critically ill subjects. The AE profile is typical of this critically

ill high risk pediatric population following major cardiac and noncardiac surgery. The most frequently reported AEs were hypotension, agitation, and bradycardia. Hypotension and bradycardia are considered to have been influences of α2 agonists. Two SAEs that occurred under study treatment (myocarditis and apnea) were reported in 2 subjects and were judged to be "Possibly related" or "Probably related" to dexmedetomidine.

Diaz et al. reported the PK of dexmedetomidine when given at a loading dose of 1 μg/kg over 10 minutes followed by titrated infusion at a dose of 0.2 to 0.7 μg/kg/h over an average of 18.8 hours in 10 subjects who underwent cardiac surgery (aged 4 months to 7.9 years)[21]. Mean CL was 0.58±0.14 L/kg/h, (correspond to approximately 40 L/h in a 70 kg adult), V_{ss} was 1.53±0.37 L/kg, and $t_{½}$ was 2.65±0.88 hours. No treatment-related SAEs were reported.

A phase 1, single-center, dose-escalation study regarding PK and PD (Study CHOP) was conducted in infants (aged 1 month to 2 years) requiring postoperative mechanical ventilation with tracheal intubation immediately after cardiac surgery. Subjects were randomized to one of the following 3 dose levels: low dose (0.35 μg/kg bolus, 0.25 μg/kg/h infusion), intermediate dose (0.7 μg/kg bolus, 0.5 μg/kg/h infusion), or high dose (1 μg/kg bolus, 0.75 μg/kg/h infusion). Both area under plasma concentration-time curve from time zero to infinity (AUC_{inf}) and C_{max} of dexmedetomidine were dose-proportional in a dose range of 0.25 to 0.75 μg/kg/h. In the 3 dexmedetomidine dose groups, dose-dependent increases were observed in mean plasma concentration, area under plasma concentration-time curve from zero to time of last measurable concentration (AUC_{last}), and AUC_{inf}. No notable differences in CL or CL_W by age were observed in all dose groups. In all of 38 subjects who received at least 1 dose of the investigational product experienced at least 1 AE, and 33 subjects experienced at least 1 AE that was judged to be "Related" to treatment.

Zuppa et al. investigated the PK of dexmedetomidine in infants aged 1 month to 2 years old, following cardiac surgery with CPB[22]. In open-label settings, dexmedetomidine was administered at the following 3 dose levels: 0.35 μg/kg bolus over 20 minutes followed by 0.25 μg/kg/h, 0.7 μg/kg bolus over 20 minutes followed by 0.5 μg/kg/h, or 1 μg/kg bolus over 20 minutes followed by 0.75 μg/kg/h. The dose levels were titrated for 24 hours based on a target sedation level according to the UMSS. PK data were obtained from 36 subjects. V_{ss} were 4.0 L/kg, 3.7 L/kg, and 5.3 L/kg in the high dose, medium dose, and low dose groups, respectively, which were higher than in older children and adults. Mean CLs were 1.4 L/h/kg, 1.2 L/h/kg, and 1.1 L/h/kg in the low dose, medium dose, and high dose groups, respectively, which were also higher than in older children. $t_{½}$ was 2.12 to 3.05 hours, comparable to that seen in the Diaz study.[21] One SAE possibly related to treatment was reported.

1.5. Rationale for This Study

Sedation is an important factor in the management of critically ill subjects. Sedation control is an essential element not only for adult patients, but also for infants and children. In current medical care, it is common to combine midazolam with morphine or fentanyl for sedation and analgesia in pediatric patients, but this can induce respiratory depression and make it difficult to manage the patient.

In adults, the efficacy and safety of dexmedetomidine hydrochloride have been established, and it is widely used as a drug for "Sedation during and after mechanical ventilation in the intensive care setting". Although no indications have been approved, DA-9501 is used for sedation in pediatric intensive care, and indications for the drug and its dosage and administration are also described in the Japanese guidelines. Further, although having not approved as indications in the U.S., the pharmacology, PK, and safety studies in juvenile animals, and PK studies and efficacy/safety studies in infants/children have been conducted.

Also, taking into account the data of pediatric PK studies in the U.S., the maximum maintenance dose for pediatric subjects in this study was set to be a dose at which the predicted steady-state plasma concentration of dexmedetomidine in children does not exceed the steady-state plasma drug concentration at the maximum maintenance dose for adults.

Taking into account the above-mentioned situations, it was considered appropriate to plan a study to obtain approval of pediatric indications for dexmedetomidine in Japan.

1.5.1. Study Population

Based on the indications for this drug 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 are some cases of the use of dexmedetomidine in patients aged <45 weeks CGA, but in these ages, usual sedative is not used or this drug is not the first choice even when sedation is required and the main target subjects were considered to be patients 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 patients requiring sedation in both surgical subjects and medical ICU subjects, and therefore it was made possible to enroll both patient 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 GGA to <17 years old)".

1.5.2. Dose Levels and Infusion Rates

Initial loading dose

It is assumed that dexmedetomidine would have an influence on circulation dynamics when an initial loading dose is given. It was considered not always necessary to promptly increase the plasma drug concentration by giving an initial loading dose in sedation management in the ICU.

Starting dose for maintenance infusion

In a survey in pediatric intensive care specialists, it was recommended to start maintenance infusion from a low dose in children. Taking into account this survey, the starting dose for maintenance infusion was set to be 0.2 μg/kg/h.

Maximum maintenance dose

In a clinical study conducted in pediatric subjects in the U.S., no clear relationship was demonstrated between the plasma drug concentration and sedative effect, but the efficacy and safety of dexmedetomidine were demonstrated at a plasma concentration of 0.3 to 1.25 ng/mL (0.2 to 0.7 μg/kg/h) in healthy adults. For setting the dosage and administration of this drug for pediatric subjects, effective plasma concentrations in adults were referred to on the assumption that there would be no much difference in response to dexmedetomidine between children and adults. Also, the maximum maintenance dose for pediatric subjects in this study was set to be a dose at which the predicted steady-state plasma concentration of dexmedetomidine in children does not exceed the steady-state plasma drug concentration at the maximum maintenance dose for adults (0.7 μg/kg/h).

The dexmedetomidine CL_w obtained in a U.S. study showed that the predicted steady-state plasma drug concentration at a maintenance dose of 1.4 μg/kg/h in children aged 1 month to <6 years old corresponded to that at a dose of 0.7 μg/kg/h in adults and that the predicted plasma drug concentration at a maintenance dose of 1.0 μg/kg/h in children aged ≥6 years old corresponded to that at a dose of 0.7 μg/kg/h in adults.

The dosage and administration in this study are within the range of dosage and administration in the clinical study conducted in the U.S. In these studies, there have been no reports of SAEs attributable to dexmedetomidine. Also, in the literature on sedation under pediatric intensive care, it was reported that dexmedetomidine was used safely at 1.0 μg/kg/h, 1.4 μg/kg/h or higher as an adjustment range of maintenance dose levels. But it was decided that the dose level would be increased in consideration of tolerability when using a dose level exceeding 1.0 μg/kg/h described in the Japanese guidelines.

1.6. Risks/Benefits

This study is a multi-center, single-arm, open-label study with the objective of evaluating the efficacy, safety, and PK of this drug when given as continuous infusion of up to 1.4 μg/kg/h in pediatric ICU patients ≥45 weeks CGA to <17 years old. Based on the data of the pediatric PK study in the U.S. and the safety data that have been obtained to date, no specific risks to infant/pediatric patients have been identified compared to adults. In clinical practice in Japan, this drug has been used in children as well. The use of this drug as a sedative is described in guidelines such as the "Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases" and the "Guidelines for the use of Anesthesia and Anesthesia related Drugs". Further, there was a request for pediatric indications for dexmedetomidine hydrochloride from academic societies at the start of the "Council for Pediatric Pharmacotherapy", and in consideration of these academic society requests as well as current medical practice in Japan, it is considered appropriate to conduct this study.

Complete information for this compound may be found in the single reference safety document (SRSD), which for this study is the Investigator's brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

To evaluate the efficacy, safety, and PK of dexmedetomidine given as continuous IV infusion in pediatric subjects (≥45 weeks GGA to <17 years old) requiring sedation under intensive care.

2.2. Endpoints

2.2.1. Primary Efficacy Endpoint

The following item for the period from the start of dosing of the investigational product to 24 hours of dosing or to the end of mechanical ventilation (when mechanical ventilation ends within 24 hours of dosing of the investigational product):

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

[Rationale for setting of primary efficacy endpoint]

This efficacy endpoint was set up to judge whether sedation management can be performed with this drug alone without additional administration of other sedative (midazolam) in the subjects of the study.[15] Also, in adult clinical studies in Japan and overseas that investigated the efficacy of dexmedetomidine within 24 hours of dosing under intensive care, a significant difference was seen between the dexmedetomidine dosing group and placebo dosing group when this primary efficacy endpoint was used.[15] And in a U.S. pediatric dose-comparative study of dexmedetomidine within 24 hours of dosing (DEX-08-05), this primary efficacy endpoint was also used, and although no significant difference was seen, a difference was seen in efficacy percentage between the low dose group and high dose group. Therefore, the endpoint was judged appropriate as the primary endpoint for this study.

2.2.2. Secondary Efficacy Endpoints

The following items for the period from the start of dosing of the investigational product to 24 hours of dosing or to the end of mechanical ventilation (when mechanical ventilation ends within 24 hours of dosing of the investigational product):

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

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 investigational product to the end of mechanical ventilation in subjects whose period of dosing of the investigational product exceeds 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 investigational product

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 investigational product:

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

9. Total amount of rescue sedative/analgesic

The following item for the period from the start of dosing of the investigational product to the end of mechanical ventilation:

10. Time until the end of mechanical ventilation

[Rationale for setting of secondary efficacy endpoints]

1. This efficacy endpoint was set up to investigate the analgesic effect of dexmedetomidine for the period from the start of dosing of the investigational product to 24 hours of dosing or to the end of mechanical ventilation.

2. This efficacy endpoint was set up to investigate the sedative/analgesic effects of dexmedetomidine for the period from the start of dosing of the investigational product to 24 hours of dosing or to the end of mechanical ventilation.

3. This efficacy endpoint was set up to investigate the sedative effect of dexmedetomidine for the period from the start of dosing of the investigational product to 24 hours of dosing or to the end of mechanical ventilation.

4. This efficacy endpoint was set up to investigate the sedative effect of dexmedetomidine in subjects whose period of dosing of the investigational product exceeds 24 hours.

5. This efficacy endpoint was set up to investigate the analgesic effect of dexmedetomidine in subjects whose period of dosing of the investigational product exceeds 24 hours.

6. This efficacy endpoint was set up to investigate the sedative/analgesic effect of dexmedetomidine in subjects whose period of dosing of the investigational product exceeds 24 hours.

7. This efficacy endpoint was set up to investigate the sedative effect of dexmedetomidine in subjects whose period of dosing of the investigational product exceeds 24 hours.

8. This efficacy endpoint was set up to investigate the sedative effect of dexmedetomidine after the end of mechanical ventilation.

9. This efficacy endpoint was set up to investigate drugs that seem to affect the sedative/analgesic effects.

10. This efficacy endpoint was set up to investigate the sedative effect of dexmedetomidine for the period from the start of dosing of the investigational product to 24 hours of dosing or to the end of mechanical ventilation.

2.2.3. Safety Endpoints

- Adverse events[a]

- Vital signs (blood pressure, heart rate, respiratory rate), percutaneous oxygen saturation (SpO_2), end-tidal carbon dioxide ($ETCO_2$), core body temperature, and body weight

- Laboratory test values

- Total Input/Output Fluid Volume

- Occurrence of withdrawal symptoms (presence/absence of hypertension, tachycardia, or agitation symptoms after the end of dosing of the investigational product)

- Electrocardiogram (ECG)

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[a] The following symptoms at the surgery site are considered common surgically-related events and are not to be reported as AEs:
Bleeding, bruising, itching, redness, swelling, numbness, tingling, burning sensation, pain, infection and rupturing of incision stitches.

Changes in laboratory test values that are normally observed after surgery do not need to be evaluated as AEs based on the physician's judgment, even if the values are outside the reference range.
Bradycardia, hypotension, and respiratory depression are to be reported as AEs if the pulse rate, blood pressure level, and respiratory rate are below the range specified for each age.

[b] Not approved in Japan

CCI [redacted]

[redacted]

3. STUDY DESIGN

This study is 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 continuous IV infusion in pediatric subjects ≥45 weeks CGA to <17 years old.

Figure 1. Elective Surgical Subjects

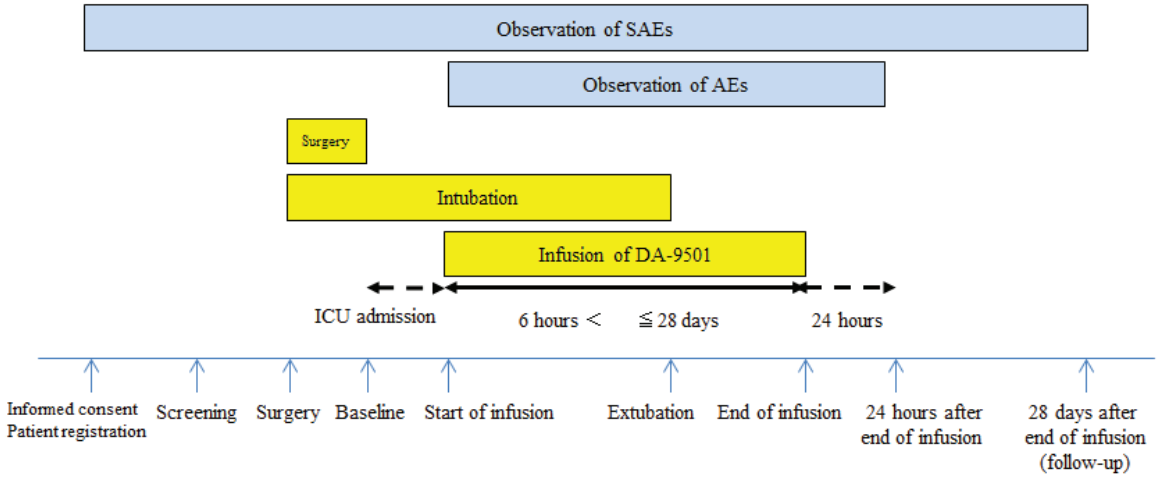
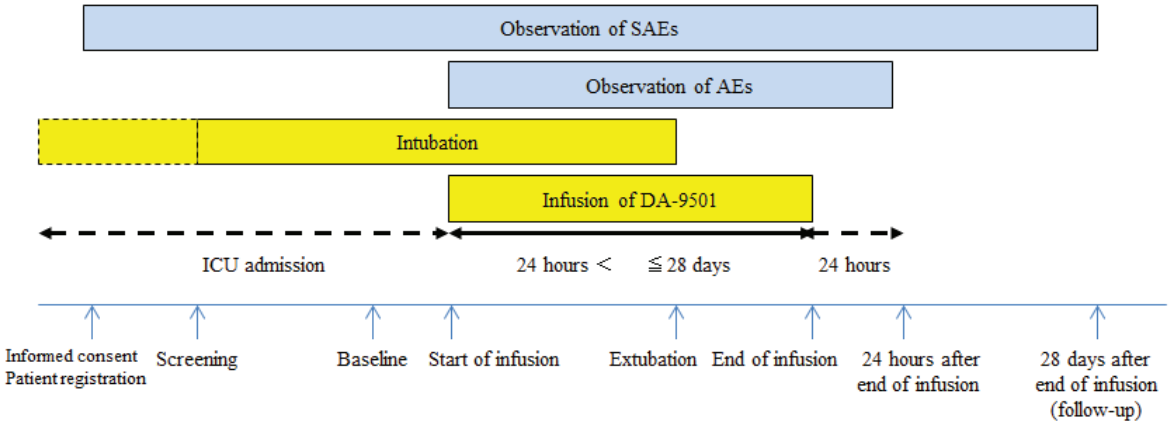


Figure 2. Medical ICU Subjects



4. SUBJECT SELECTION

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

4.1. Inclusion Criteria

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

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

1. Subjects whose consent is obtained in writing prior to the clinical trial from a guardian after a full explanation. For subjects 7 years and older, it is desirable that an informed assent is also obtained from the pediatric subject him/herself when possible.

2. Subjects aged ≥45 weeks CGA to <17 years old at time of consent. No restriction on sex of subject.

3. [Elective surgical subjects] Subjects classified as American Society of Anesthesiologists (ASA) (ASA physical status classification) Class I to III by preoperative diagnosis.

Table 2. ASA Classification[23]

I	A normal healthy patient
II	A patient with mild systemic disease Moderate obesity, elderly, diabetes mellitus with dietary restrictions, mild hypertension, chronic lung disease
III	A patient with severe systemic disease that interferes with activities Morbid obesity, highly restrictive heart disease, angina pectoris, old myocardial infarction, insulin-dependent diabetes mellitus, moderate to severe lung disease
IV	An almost bedridden patient with severe systemic disease that is a constant threat to life Organic heart disease associated with heart failure, unstable angina pectoris, refractory arrhythmia, severe lung/kidney/liver/endocrine disease
V	A moribund patient who is not expected to survive for 24 hours without the operation Ruptured aortic aneurysm associated with shock, severe lung infarction, head injury associated with brain hypertension

4. [Elective surgical subjects] Subjects who require at least 6 hours of respiratory management with intubation under intensive care from immediately after surgery and are anticipated to require sedation.

5. [Medical ICU subjects] Subjects who require at least 24 hours of respiratory management with intubation under intensive care and are anticipated to require sedation. For medical ICU subjects, sedatives used prior to treatment with the investigational product should be discontinued before the start of treatment with the investigational product.

6. If a subject is a female of childbearing potential, she should not be pregnant or possibly pregnant, or lactating.

4.2. Exclusion Criteria

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

1. Subjects who are judged by investigator or sub-investigator to have a neurological disease that will make sedation assessment difficult, such as:

   - Subjects with brain damage which is expected to increase intracranial pressure due to trauma or central nervous system disease.
   - Subjects with cerebral palsy, autism, severe mental retardation, etc.
   - Subjects with paralysis due to continuous administration of a muscle relaxant or due to a spinal injury of class T5 or higher.

2. Subjects with 2nd or 3rd degree heart block in the tests at the screening period (excluding subjects using a pacemaker).

3. Subjects with any of the following low blood pressure levels[24] in the tests at the screening period:

   - Age ≥45 weeks CGA to <1 year old: Systolic Blood Pressure (SBP) <70 mmHg
   - Age ≥1 year to <10 years old: SBP <70 + (2 x age in years) mmHg
   - Age ≥10 years to <17 years old: SBP <90 mmHg

4. Subjects with bradycardia (≤10th centile of heart rate for healthy children) in the physical examination at screening period shown in Table 3.

Table 3. Centiles of Heart Rate (HR) in Children[25]

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

5. Subjects with ALT ≥100 U/L in the laboratory tests at the screening period.

6. Subjects in whom dexmedetomidine or other α2 receptor agonists, α2 receptor antagonists and drug that may be used in this study are contraindicated.

7. Subjects who may need a sedative or analgesic (including narcotics) other than dexmedetomidine, midazolam or fentanyl during treatment with the investigational product.

8. Subjects who have acute febrile illness (with a temperature [core or tympanic] ≥38°Centigrade) at the screening period.

9. Subjects who received other investigational product within 30 days before baseline or subjects who will participate in other study that uses an investigational product during the study period.

10. Subjects who received dexmedetomidine within 48 hours before baseline

11. Subjects who, in the opinion of the investigator or sub-investigator, may be at increased risk due to the conduct of the study or may have a disease or factor which will probably preclude the obtainment of sufficient study data.

12. Subjects for whom, in the opinion of the investigator or sub-investigator, risks involved with administration of dexmedetomidine outweigh its benefits (e.g., >2 doses of vasopressor due to cardiogenic shock).

13. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are Sponsor's employees directly involved in the conduct of the study.

4.3. Criteria Lifestyle Guidelines

All fertile male subjects and female subjects of pregnancy potential who are sexually active and at risk for pregnancy must agree to use a highly effective contraceptive method consistently and properly during the period of treatment with the investigational product and for at least 28 days after the last dose of the investigational product. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected a contraceptive method appropriate for the individual subject or subject's male or female partner from among permitted contraceptive methods (See below), and also instruct the subject to use the method consistently and properly. Subjects need to affirm that they meet the criteria for correct use of at least 1 of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject or the subject's partner.

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

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

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

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

4. Male sterilization with absence of sperm in the postvasectomy ejaculate.

5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Female partner who meets the criteria for non-childbearing potential, as described below:

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

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; a serum follicle stimulating hormone (FSH) level confirming the post menopausal state.
- Women who have not yet had her first menstrual period

All other female subjects (including females with tubal ligations) will be considered to be of childbearing potential.

[b] Not approved in Japan

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

4.4. Sponsor's Appropriately Qualified Medical Personnel

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational site, and contact details for a contact center in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational site.

5. STUDY TREATMENTS

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

5.1. Allocation to Investigational Product

As this study is a single-arm study, no allocation will be performed.

5.2. Medication Compliance

Administration of the investigational product will be performed by persons who are appropriately designated at the investigational site.

5.3. Investigational Product

Name: DA-9501

Generic name: Dexmedetomidine hydrochloride (JAN)

Chemical name: (+)-(*S*)-4-[1-(2, 3-dimethylphenyl) ethyl]-1H-imidazole monohydrochloride

5.3.1. Dosage Form and Packaging Form of Investigational Product

Content/Dosage Form: A single vial contains an injection solution with 2 mL of dexmedetomidine hydrochloride solution (100 μg/mL as dexmedetomidine) dissolved in physiological saline.

5.3.2. Preparation and Dispensing

For instructions on how to prepare the investigational product for administration, see the IP manual (Investigational Product Manual). Investigational product should be 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.

5.4. Administration of Investigational Product

No initial loading dose will be given. Baseline body weight will be used to determine the dose of the investigational product.

≥45 weeks CGA to <6 years old

Maintenance infusion will be started at 0.2 μg/kg/h. The infusion rate will be adjusted within a range of 0.2 to 1.4 μg/kg/h according to the pediatric subject's sedative state.

≥6 years to <17 years old

Maintenance infusion will be started at 0.2 μg/kg/h. The infusion rate will be adjusted within a range of 0.2 to 1.0 μg/kg/h according to the pediatric subject's sedative state.

[Dosing Duration]

Dosing of dexmedetomidine will be started after the patient is admitted to the intensive care unit. Dosing of dexmedetomidine may be continued after extubation as needed. The dosing duration will be at least 6 hours in elective surgical subjects and at least 24 hours in medical ICU subjects for up to 28 days.

[Points to note when increasing the infusion rate of the investigational product]

If the investigator or sub-investigator deems that the subject has not reached an adequate sedative state or the SBS score specified in the protocol is +1 or +2, the investigator or sub-investigator will increase the infusion rate of the investigational product. While an increase of 0.1 μg/kg/h or more is possible when increasing the infusion rate, the infusion rate should be gradually increased over 3 to 4 minutes or longer per 0.1 μg/kg/h.

[Points to note at end of dosing of the investigational product]

If dosing of dexmedetomidine lasts longer than 24 hours at the end of dosing of the investigational product, gradual reduction of the infusion rate of dexmedetomidine will be

considered at the discretion of the investigator or sub-investigator. An example of gradual reduction is gradually reducing the infusion rate of dexmedetomidine over about 4 hours or longer. Withdrawal symptoms may occur following sudden discontinuation of dosing after long-term treatment (See the package insert of this drug). Tachycardia, hypertension, agitation, and vomiting after discontinuation of this drug are likely to be such withdrawal symptoms. A publication reported that these symptoms can occur easily in patients for whom the total dose of this drug is 8.5 μg/kg or more, and therefore it is necessary to reduce the dose slowly (by 0.1 μg/kg/h, every 12 hours when the drug is used for a long period)[26]. For example, it is said that the infusion rate of this drug should be gradually reduced over 4 hours or longer, but if dosing of the drug is to be discontinued, the treatment period for the subject should be considered, and according to the circumstances, the dose reduction period should be carefully considered.

[Target Sedation Depth]

The target sedation depths during mechanical ventilation and after extubation are shown below.

- During mechanical ventilation: SBS −2 to 0
- After extubation: SBS −1 to 0

5.5. How to Deal With Overdose

Overdose will be dealt with according to the Investigator's Brochure and/or package insert of dexmedetomidine.[27]

5.6. Investigational Product Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements. Investigational product should be stored in its original container and in accordance with the label. Regarding the storage conditions of the investigational product which is once diluted, see the written procedures for the management of investigational products and the IP manual.

Storage conditions stated in the SRSD (Investigator's Brochure in the case of this study) will be superseded by the storage conditions stated in the label of the investigational product.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

5.7. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies.

5.7.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Sponsor, and all destruction must be adequately documented.

5.8. Concomitant Therapies

All concomitant medications used between 48 hours before the start of infusion of the investigational product and 24 hours after the end of infusion of the investigational product (date and time of administration, dosage/administration, route of administration, and reason for administration) will be recorded in the case report form (CRF). Drugs used during surgery may be described as the total dose given during surgery. In addition, non-drug treatment from 48 hours before the start of dosing of the investigational product to 24 hours after the end of dosing of the investigational product will be recorded.

Any other sedatives used prior to the start of infusion of the investigational product should be discontinued.

5.8.1. Prohibited Concomitant Drugs

Between the start of infusion of the investigational product (for dexmedetomidine, 48 hours before the start of infusion of the investigational product) and the end of dosing of the investigational product, concomitant uses of the following drugs will be prohibited. When continuing dosing of dexmedetomidine after withdrawal from mechanical ventilation, it is acceptable to use standard analgesics at each medical institution if necessary.

1. Sedatives/analgesics (including narcotics) other than dexmedetomidine, midazolam, and fentanyl. Use of non-steroidal anti-inflammatory drugs for the management of patient ductus arteriosus will be allowed but should be appropriately described in the CRF.

2. Continuous infusion of muscle relaxants

3. Drugs contraindicated for coadministration with dexmedetomidine, midazolam, and fentanyl

4. α2 receptor agonists other than dexmedetomidine and α2 receptor antagonists

[Rationale for setting of prohibited concomitant drugs]

These criteria were set up to avoid any influence on the sedation/analgesia assessment.

1. Concomitant uses are prohibited because of influence on the sedation/analgesia assessment.

2. Concomitant uses are prohibited because of possible influence on the sedation assessment.

3. Prohibition of concomitant uses was set up in consideration of the subject's safety.

4. Concomitant uses are prohibited because of possible influence on the sedation assessment.

5.8.2. Restricted Concomitant Drugs

Between the start of infusion of the investigational product and 24 hours after the end of infusion of the investigational drug, the following drugs will be restricted.

Continuous infusion of fentanyl

If discontinuation of continuous infusion of fentanyl is considered likely to cause disadvantage to the subject, fentanyl may be continuously used. It is desirable not to change the infusion rate of fentanyl during administration of dexmedetomidine.

Muscle relaxants

Temporary use of muscle relaxants will be allowed at the time of painful or irritative procedures, but they will not be used at the time of sedation assessment.

5.9. Rescue Sedatives and Rescue Analgesics

If the investigator or sub-investigator deems that the subject has not reached an adequate sedative state or the SBS score specified in the protocol is +1 or +2, the investigator or sub-investigator will increase the infusion rate of the investigational product. While an increase of 0.1 μg/kg/h or more is possible when increasing the infusion rate, the infusion rate should be gradually increased over 3 to 4 minutes or longer per 0.1 μg/kg/h.

If sedation is needed, it is possible to administer a rescue sedative (midazolam) based on the data of SBS and the investigator or sub-investigator's judgment, but it is desirable to judge the necessity of a rescue sedative after increasing the infusion rate of dexmedetomidine (maximum maintenance dose: 1.4 μg/kg/h for ≥45 weeks GA to <6 years old; 1.0 μg/kg/h for ≥6 years to <17 years old) and performing the sedation assessment again.

A rescue analgesic (fentanyl) will be used at the time of painful or irritative procedures based on the investigator or sub-investigator's judgment. Continuous infusion of fentanyl may be used for the treatment of pain or irritation (See 5.8.2 restricted concomitant drugs). Bolus infusion of fentanyl should not be performed at the time of sedation assessment.

If the SBS score is <−2, the infusion rate may be deceased to the lower limit maintenance infusion rate (0.2 μg/kg/h). If judged necessary by the investigator or sub-investigator, the infusion rate can be decreased below the lower limit maintenance infusion rate or the infusion can be stopped.

If a rescue sedative or rescue analgesic is used between the start of infusion of the investigational product and 24 hours after the completion of infusion of the investigational product, this should be appropriately described in the CRF.

Rescue Sedative: Midazolam

Midazolam will be intravenously administered at a dose of 0.05 to 0.2 mg/kg over 2 to 3 minutes according to the package insert based on the investigator or sub-investigator's judgment. Sedation assessment will be performed immediately before infusion of the rescue sedative and at 5±2 minutes after infusion.

In subjects who need 5 or more doses of the rescue sedative per hour despite an increase of the infusion rate up to the maximum maintenance infusion rate of dexmedetomidine, the study will be discontinued and other sedation management method will be used.

Rescue Analgesic: Fentanyl

Pain/discomfort will be dealt with by increasing the infusion rate not exceeding the upper limit for dexmedetomidine, based on the investigator or sub-investigator's judgment. Bolus infusion of fentanyl will be based on the investigator or sub-investigator's judgment (1 to 2 μg/kg). Sedation assessment will be performed immediately before infusion of the rescue analgesic and at 5±2 minutes after infusion.

6. STUDY PROCEDURES

6.1. Screening (1 to 7 Days Before Start Date of Treatment With Investigational Product)

Screening will be performed 1 to 7 days before the start date of treatment with the investigational product for the following items:

- Informed consent

Prior to the study, a written consent will be obtained from the guardian of the subject after a full explanation. For subjects 7 years and older, it is desirable that an informed assent is also obtained from the pediatric subject him/herself when possible. If the signature of the subjects cannot be obtained or if an assent was obtained orally without using a document, it should be described, in the consent form signed by the guardian, that an assent was obtained from the subject.

- Subject registration

The investigator or sub-investigator will confirm that the subject matches the subject background and inclusion criteria and does not meet the exclusion criteria at the start of the study, and then promptly register the subject via FAX with the center designated by the sponsor.

- Checking of inclusion/exclusion criteria
- Subject background (date of birth, weeks of CGA [only when <1 year old], gender, race, etc.)
- Checking of noteworthy medical history/complications
- Checking of surgery/actions, primary disease name, etc.
  - Elective surgical subjects: Checking of primary disease name and ASA classification
  - Medial ICU subjects: Checking of primary disease name, status of intubation during sedation and reason for intubation, start date/time and mode of ventilator, and date/time of ICU admission
- Physical examination
- Height, body weight, core body temperature (All of them will be measured to first decimal place)
- Vital signs (BP, HR, RR), percutaneous oxygen saturation (SpO_2), and end-tidal carbon dioxide ($ETCO_2$)
- 12-lead ECG
- Laboratory tests
- Pregnancy test (to be performed only in women of childbearing potential)
- Checking of concomitant drugs and non-drug treatment

6.2. Treatment Period

6.2.1. Baseline (Start Date of Treatment With Investigational Product)

Baseline will be the start date of treatment with the investigational product, and the following items will be performed before the start of treatment with the investigational product. In elective surgical subjects, the items will be performed after surgery unless otherwise particularly described.

- Checking of surgery/actions, primary disease name, etc.
  - Elective surgical subjects: Checking of date of surgery, type of procedure, start and end date/time of surgery, status of intubation during sedation and reason for intubation, anesthetics and analgesics used for surgery, start date/time and mode of ventilator, and date/time of ICU admission
- Physical examination
- Body weight and core body temperature (All of them will be measured to first decimal place)

  Baseline body weight will be used to determine the dose of the investigational product.
- Vital signs (BP, HR, RR), SpO_2, and $ETCO_2$
- 12-lead ECG and laboratory tests (to be performed only in elective surgical subjects)

  In patients undergoing heart surgery, these items will be performed after surgery and within 90 minutes before the start of dosing of the investigational product.
- Sedation assessment
- Checking of concomitant drugs and non-drug treatment
- Checking of SAEs
- Start of ECG monitoring (to be continued until 24 hours after the end of dosing of the investigational product)

6.2.2. From Start of Dosing to 24 Hours After Dosing or End of Mechanical Ventilation

- Core body temperature (See section 7.2.2; To be measured to first decimal place)
- Vital signs (BP, HR, RR), SpO_2, and $ETCO_2$ (See section 7.2.4)
- Checking of setting of ventilator (If the mode of the ventilator was changed, the mode will be recorded)

- Sedation assessment (See section 7.1.2)
- Dosing of investigational product (See section 5.4)
- Checking of dosing of rescue sedative
- Checking of dosing of rescue analgesic
- Checking of concomitant drugs and non-drug treatment
- Checking of AEs/SAEs
- Blood sampling for plasma drug concentration (See section 7.3)
- Laboratory tests (to be performed as needed)
- ECG monitoring (to be continued from before the start of dosing of the investigational product to 24 hours after the end of dosing of the investigational product)

6.2.3. From 24 Hours After Dosing to End of Mechanical Ventilation

- Core body temperature (See section 7.2.2; To be measured to first decimal place)
- Vital signs (BP, HR, RR), SpO_2, and $ETCO_2$ (See section 7.2.4)
- Checking of setting of ventilator (If the mode of the ventilator was changed, the mode will be recorded)
- Checking of end date/time of ventilator
- Sedation assessment (See section 7.1.2)
- Dosing of investigational product (See section 5.4)
- Checking of dosing of rescue sedative
- Checking of dosing of rescue analgesic
- Checking of concomitant drugs and non-drug treatment
- Checking of AEs/SAEs
- Blood sampling for plasma drug concentration (See section 7.3)
- Laboratory tests (to be performed as needed)

- ECG monitoring (to be continued from before the start of dosing of the investigational product to 24 hours after the end of dosing of the investigational product)

6.2.4. From End of Mechanical Ventilation to End of Dosing of Investigational Product

- Core body temperature (See section 7.2.2; To be measured to first decimal place)
- Vital signs (BP, HR, RR), SpO_2, and $ETCO_2$ (See section 7.2.4)
- Checking of Total Input/Output Fluid Volume (from the start to end of dosing of the investigational product)
- Sedation assessment (See section 7.1.2)
- Dosing of investigational product (See section 5.4)
- Checking of dosing of rescue sedative
- Checking of dosing of rescue analgesic
- Checking of concomitant drugs and non-drug treatment
- Checking of AEs/SAEs
- Blood sampling for plasma drug concentration (See section 7.3)
- Laboratory tests (to be performed as needed)
- ECG monitoring (to be continued from before the start of dosing of the investigational product to 24 hours after the end of dosing of the investigational product)

6.2.5. 24 Hours (± 5 min) After End of Dosing of Investigational product

- Checking of date/time of ICU discharge (if the subject was discharged)
- Physical examination
- Body weight and core body temperature (to be measured to first decimal place)
- Vital signs (BP, HR, RR), SpO_2, and $ETCO_2$
- 12-lead ECG and laboratory tests
- End of ECG monitoring
- Sedation assessment
- Checking of concomitant drugs and non-drug treatment

- Checking of AEs/SAEs
- Blood sampling for plasma drug concentration (See section 7.3)

6.2.6. At Early Discontinuation of Study

For subjects who have discontinued the study after the start of dosing of the investigational product, all of the tests planned to be performed at 24 hours after the end of dosing of the investigational product will be performed at the time of the early discontinuation in principle and those will be evaluated. Also, all of the observation items up to that time point will be recorded, and the reason for the discontinuation will be clearly stated in the CRF.

6.3. Follow-up Period

The follow-up period will be from the observation at 24 hours after the end of dosing of the investigational product to 28 days after the end of dosing. SAEs that occur during this period will be reported to the sponsor according to the procedure described in section 8.

6.4. Criteria and Procedure for Subject Withdrawal From Study

The investigator or sub-investigator will withdraw a subject from the study if the subject meets any of the following criteria.

1. If any of the following AEs occurred.

Bradycardia

Bradycardia (Table 3: 10th percentile or less of heart rate) does not respond to treatments, including administration of atropine, which are usually done in the intensive care unit or bradycardia is clinically relevant.

Hypotension

Any of the following hypotension levels does not respond to treatments, including infusion solution, and vasopressors/inotropic agents, that are usually done in the intensive care unit or hypotension is clinically relevant.

- Age ≥45 weeks CGA to <1 year old: SBP <70 mmHg
- Age ≥1 year to <10 years old: SBP <70 + (2x age in years) mmHg
- Age ≥10 years to <17 years old: SBP <90 mmHg

Respiratory Depression

If respiratory depression persists at the 10th percentile or less of respiratory rate (Table 4) and does not respond to treatments that are usually done in the intensive care unit or respiratory depression is clinically relevant.

Table 4. Centiles of Respiratory Rate (RR) in Children[25]

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

Paradoxical Reactions

If any of the following paradoxical reactions occurred.

[≥45 weeks CGA to <8 years old]

It is not possible to explain the subject's medical condition as other than a paradoxical reaction, and there is agitation or crying out loud to the extent that cannot be controlled through normal intervention.

[≥8 years to <17 years old]

It is not possible to explain the subject's medical condition as other than a paradoxical reaction, and there is severe emotional volatility or aggressive behavior to the extent that cannot be controlled through normal intervention. Examples include violence by the subject or obstruction of medical professionals, etc.

2. It is necessary to give 5 doses or more of a rescue sedative (midazolam) per hour in order to maintain an adequate sedation level despite an increase of the infusion rate up to the maximum maintenance infusion rate of investigational product.

3. The subject or his/her guardian requests withdrawal from the study.

4. The investigator or sub-investigator judges that withdrawal from the study is the best interest of the subject (e.g. due to occurrence of an AE).

5. The subject's medical condition changes and a deeper sedation level or continuous administration of muscle relaxant is required.

6. The subject no longer requires sedation by continuous IV and dosing of dexmedetomidine is less than 6 hours.

7. Any other reason for which the investigator or sub-investigator judges continuation of the study to be difficult.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

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

7.1. Efficacy Evaluation

7.1.1. Rescue Sedatives and Rescue Analgesics

See section 5.9.

7.1.2. Sedation Assessment

Assessment Scale of Sedation Depth

Sedation depth will be assessed by using the State Behavioral Scale (SBS) (Table 5).

Sedation Assessment and Target Sedation Level

The investigator, sub-investigator, or clinical research collaborator who has attended the SBS training provided by the sponsor will assess sedation depth by using SBS. The target sedation depth by SBS is –2 to 0 during mechanical ventilation and −1 to 0 after extubation. The assessment points will be as follows.

[Prior to dosing to end of dosing of investigational product]

The level will be 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 investigational product, and every 4 hours±5 minutes later than 4 hours after the start of dosing. The level will be measured every 4 hours±5 minutes from Day 2 of treatment to extubation. If the investigational product is continuously dosed after extubation, the level will be measured every 4 hours±5 minutes until the end of dosing of the investigational product.

[At the time of extubation]

The level will be measured at 5±2 minutes before extubation, and at 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.

[End of dosing of investigational product to 24 hours after end of dosing of investigational product]

The level will be measured at the end of dosing of the investigational product (+5 minutes), at 1 hour±5 minutes, 2 hours±5 minutes and 4 hours±5 minutes after the end of dosing of the investigational product, and every 4 hours±5 minutes later than 4 hours after the end of dosing of the investigational product.

[At the time of changing the infusion rate of investigational product]

The level will be measured at 5±2 minutes immediately before changing the infusion rate of the investigational product and at 5±2 minutes after changing the rate.

[When administering a rescue sedative/analgesic]

The level will be measured at 5±2 minutes immediately before administration of the rescue sedative (midazolam) or rescue analgesic (fentanyl) and at 5±2 minutes after administration.

Table 5. State Behavioral Scale (SBS)[28]

-3	Unresponsive	No spontaneous respiratory effort
		No cough or coughs only with suctioning
		No response to noxious stimuli
		Unable to pay attention to care provider
		Does not distress with any procedures [including noxious]
		Does not move
-2	Responsive to noxious stimuli	Spontaneous yet supported breathing
		Coughs with suctioning/repositioning
		Responds to noxious stimuli
		Unable to pay attention to care provider
		Will distress with a noxious procedures
		Does not move/occasional movement of limbs or shifting of position
-1	Responsive to gentle touch or voice	Spontaneous but ineffective nonsupported breaths
		Coughs with suctioning/repositioning
		Responds to touch/voice
		Able to pay attention but drifts off after stimulation
		Distresses with procedures
		Able to calm with comforting touch or voice when stimulus is removed
		Occasional movement of limbs or shifting of position
0	Awake and able to calm	Spontaneous and effective breathing
		Coughs when repositioned/occasional spontaneous cough
		Responds to voice/no external stimulus is required to elicit response
		Spontaneously pays attention to care provider
		Distresses with procedures
		Able to calm with comforting touch or voice when stimulus is removed
		Occasional movement of extremities or shifting of position/increased movement (restless, squirming)
1	Restless and difficult to calm	Spontaneous effective breathing/having difficulty breathing with ventilator
		Occasional spontaneous cough
		Responds to voice/no external stimulus is required to elicit response
		Drifts off/Spontaneously pays attention to care provider
		Intermittently unsafe
		Does not consistently calm, despite 5-min attempt/unable to be console
		Increased movement (restless, squirming)
2	Agitated	May have difficulty breathing with ventilator
		Coughing spontaneously
		No external stimulus required to elicit response
		Spontaneously pays attention to care provider
		Unsafe (biting the endotracheal tube [ETT], pulling at catheters, cannot be left alone)
		Unable to console
		Increased movement (restless, squirming, or thrashing side-to-side, kicking legs)

7.1.3. Ventilator Setting

The start date/time and end date/time of the ventilator will be recorded. Also, if the mode of the ventilator was changed, the mode and the date/time of the change will be recorded.

7.2. Safety Evaluation

7.2.1. Physical Examination

Physical examination (medical examination) including auscultation, percussion, visual examination, palpation, etc. will be performed at screening, at baseline, and at 24 hours (±30 minutes) after dosing of the investigational product. If any change (worsening) from baseline is observed in physical findings, it will be reported as an AE.

7.2.2. Core Body Temperature

It will be measured at screening, at baseline, and subsequently, every 12 hours (±5 min) during dosing of the investigational product, at the end of dosing of the investigational product, and at 24 hours (±5 min) after the end of dosing of the investigational product.

7.2.3. Body Weight

It will be measured at screening, at baseline, and at 24 hours (±5 min) after the end of dosing of the investigational product.

7.2.4. Vital Signs (BP, HR, RR), SpO_2, and $ETCO_2$

Blood pressure (SBP and DBP), HR, RR, SpO_2, and $ETCO_2$ will be measured. The measurement points will be as follows.

[Prior to dosing to end of dosing of investigational product]

The items will be measured at screening, 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 investigational product, and every 4 hours±5 minutes later than 4 hours after the start of dosing. The items will be measured every 4 hours±5 minutes from Day 2 of treatment to extubation. If the investigational product is continuously dosed after extubation, the items will be measured every 4 hours±5 minutes until the end of dosing of the investigational product.

[At the time of extubation]

The items will be measured at 5±2 minutes before extubation, and at 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.

[End of dosing of investigational product to 24 hours after end of dosing of investigational product]

The items will be measured at the end of dosing of the investigational product (+5 minutes), at 1 hour±5 minutes, 2 hours±5 minutes and 4 hours±5 minutes after the end of dosing of the investigational product, and every 4 hours±5 minutes later than 4 hours after the end of dosing of the investigational product.

[At the time of changing the infusion rate of investigational product]

The items will be measured at 5±2 minutes immediately before changing the infusion rate of the investigational product and at 5±2 minutes after changing the rate.

[When administering a rescue sedative/analgesic]

The items will be measured at 5±2 minutes immediately before and after dosing of the rescue sedative (midazolam) and rescue analgesic (fentanyl).

7.2.5. 12-Lead ECG and ECG Monitoring

12-lead ECG will be measured at screening and at 24 hours (±30 min) after the end of dosing of the investigational product.

In elective surgical subjects, it will be performed at baseline (after surgery) as well. In patients undergoing heart surgery, it will be performed after surgery and within 90 minutes before the start of dosing of the investigational product.

Also, continuous ECG monitoring will be started prior to dosing of the investigational product, and continue until 24 hours after the end of dosing of the investigational product. All clinically significant changes observed in the ECG (e.g. arrhythmia) will be recorded as AEs.

7.2.6. Laboratory Tests; Pregnancy Test

The laboratory tests described in the table below will be performed at screening and at 24 hours (±30 min) after the end of dosing of the investigational product at the investigational site. Also, the laboratory tests during the period of treatment with the investigational product will be performed as needed.

In elective surgical subjects, it will be performed at baseline (after surgery) as well. In patients undergoing heart surgery, they will be performed after surgery and within 90 minutes before the start of dosing of the investigational product.

For female subjects of childbearing potential, a serum or urine pregnancy test with sensitivity of at least 25 mIU/mL will be performed at screening at the investigational site. A negative pregnancy test result is required before the subject may receive the investigational product.

If there occurred any laboratory test value outside the reference range in laboratory tests performed after the end of dosing of the investigational product, follow-up will be performed if the investigator or sub-investigator judges it necessary.

Table 6. Measurement Items for Laboratory Tests

Laboratory tests	Test items
Hematology test	Red blood cell count, hemoglobin content, hematocrit level, white blood cell count, neutrophil, eosinophil, basophil, lymphocyte, monocyte, stab cell, and platelet count
Blood chemistry test	Glucose, total protein, albumin, creatinine, BUN, uric acid, total bilirubin, AST/SGOT, ALT/SGPT, γ-GTP, alkaline phosphatase, sodium, potassium, magnesium, calcium, and inorganic phosphorus
Urinalysis	Specific gravity, pH, glucose, protein, occult blood, and ketone body
Pregnancy test[a]	Serum hCG test or urinary hCG test

a To be performed only in women of childbearing potential at screening.

7.2.7. Total Input/Output Fluid Volume

From the start to end of dosing of the investigational product, total input fluid volume and total output fluid volume will be recorded.

7.2.8. Adverse Events; Serious Adverse Events

AEs and SAEs will be recorded according to the procedure described in Chapter 8.

CCI [redacted]

CCI [redacted]

[redacted]

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and sponsor concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Sponsor or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious or non-serious) should be recorded on the CRF from the time the subject has taken at least 1 dose of investigational product through the subject's last visit (24 hours after the end of dosing of the investigational product in the case of this study).

8.3. Definition of an Adverse Event

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

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

Additionally, they may include the signs or symptoms resulting from:

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

AEs peculiar to this study are defined as follows.

[AEs at the surgery site]

The following symptoms at the surgery site are considered common surgically-related events and are not to be reported as AEs: Other postoperative symptoms are to be reported as AEs.

- Bleeding, bruising, itching, redness, swelling, numbness, tingling, burning sensation, pain, infection and rupturing of incision stitches.

[Changes in clinical laboratory test values associated with surgery]

Changes in laboratory test values that are normally observed in elective surgical subjects or medical ICU subjects do not need to be evaluated as AEs based on the investigator's judgment, even if the values are outside the reference range.

[Bradycardia, hypotension and respiratory depression]

Bradycardia

If a heart rate at the 10th percentile or less of heart rate (Table 3), this will be handled as an AE.

Hypotension

If blood pressure levels below the following reference blood pressure ranges are observed, they shall be handled as AEs.

- Age ≥45 weeks CGA to <1 year old: SBP <70 mmHg
- Age ≥1 year to <10 years old: SBP < 70+ (2x age in years) mmHg
- Age ≥10 years to <17 years old: SBP < 90 mmHg

Respiratory Depression

If a respiratory rate at the 10 percentile or less of respiratory rate (Table 4), this will be handled as an AE.

8.4. Medication Error

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error CRF, which is a specific version of the AE page, and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

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

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

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

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

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

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

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

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

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (×ULN) concurrent with a total bilirubin value ≥2×ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2×ULN or not available;

- For subjects with preexisting ALT OR AST OR total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3×ULN, or ≥8 ULN (whichever is smaller).

    Concurrent with

    - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased from baseline by an amount of at least 1×ULN or if the value reaches ≥3×ULN (whichever is smaller).

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

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery,

blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

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

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

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

8.8. Severity Assessment

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

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

8.9. Causality Assessment

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

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as

appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy (EDP)

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

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

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

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

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

An occupational exposure is reported to the drug safety unit within 24 hours of the investigator's awareness, using the SAE report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a CRF; however, a copy of the completed SAE report form is maintained in the investigator site file.

8.12. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/legal guardian. In addition, each study subject/legal guardian will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Sponsor is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Sponsor must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP, exposure via breastfeeding, and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Sponsor in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Sponsor to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Sponsor or its designated representative.

8.14.2. Nonserious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor's Reporting Requirements to Regulatory Authorities

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

9. STATISTICAL ANALYSES

Detailed methods of summarization and statistical analyses of data collected in this study will be described in the statistical analysis plan retained by the sponsor. In the statistical analysis plan, the plan outlined in the protocol may be modified, but for important changes related to the definition of the primary endpoint and/or its analysis, the protocol will be also revised.

9.1. Analysis Populations

Efficacy evaluation population, safety analysis population (full analysis set), and PK analysis population are defined as follows.

9.1.1. Efficacy Evaluation Population

Subjects meeting all of the following criteria will be handled as the efficacy evaluation population:

1. Subjects who did not receive any prohibited concomitant drug.

2. Subjects who received continuous IV infusion of the investigational product over at least 6 hours.

Note that time of receiving study drug excludes time of interruptions if subjects experience interruptions of study drug.

In the efficacy evaluation, this analysis population will be used for the secondary analysis, and the full analysis set will be used for the primary analysis.

9.1.2. Safety Analysis Population (Full Analysis Set)

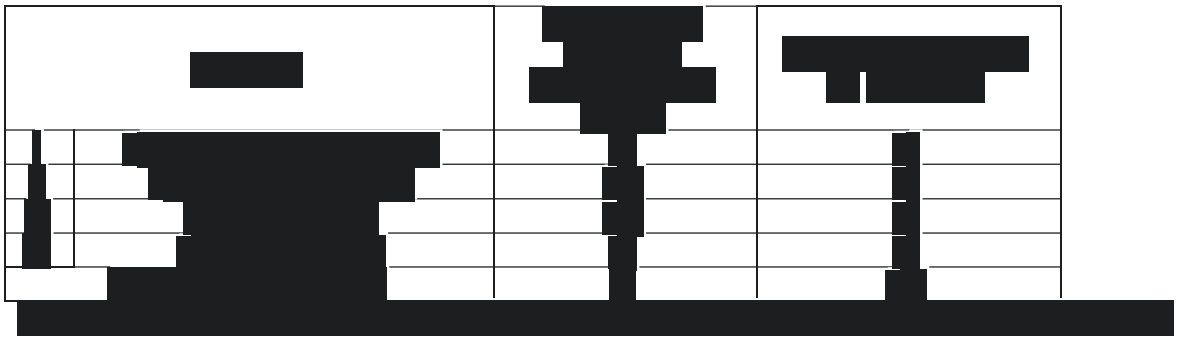
The safety analysis population (full analysis set) will be composed of all subjects who have received at least one dose of the investigational product.

Safety evaluation will use this analysis population.

CCI [redacted]

CCI [redacted]

[redacted]



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9.3. Efficacy Analysis

9.3.1. Analysis of Primary Endpoint

In the primary efficacy analysis, the efficacy percentage of dexmedetomidine defined in section 2.2.1 and its 95% confidence interval will be calculated for all subjects in full analysis set, and the 95% lower confidence limit will be compared to the threshold value (40%). A similar analysis will be also performed for the efficacy evaluation population as a secondary efficacy analysis. In addition, the efficacy percentage and the number of subjects will be summarized by age group.

9.3.2. Analysis of Secondary Endpoints

For the secondary endpoints defined in section 2.2.2, continuous variables will be summarized by using basic statistics such as mean, median, standard deviation and range. For categorical variables, the number of subjects and its percentage will be summarized. The analyses will be performed for whole subjects as well as for age groups.

9.4. Safety Analysis

Safety evaluation will be performed for items such as changes from baseline. Also, the evaluation will be summarized based on "Pfizer Data Standards (PDS)" and investigated clinically. The analyses will be performed for whole subjects as well as for age groups.

9.5. Pharmacokinetics

A population PK analysis will be performed by using data obtained in this study. The details of this analysis will be described in the population PK analysis plan, and the results of the analysis will be described in a report which will be separately prepared.

9.6. Interim Analysis

Interim analyses will be performed for the purpose of protecting the subject's safety. The details of the interim analyses will be described in statistical analysis plan and internal review committee (IRC) charter specified separately.

9.7. Data Monitoring Committee (DMC)

In this study, an IRC will be established. The IRC will be composed of 3 or more members who are not directly related to this study and will perform safety monitoring based on the internal review committee charter which are separately specified for the purpose of protecting the subject's safety. The IRC will provide advices to the sponsor regarding modifications of the protocol, temporary suspension of the study, or early discontinuation of the study from the viewpoint of safety.

9.8. Early Discontinuation of Study

The sponsor may discontinue the study either entirely or at an applicable medical institution after giving written notice at an appropriate timing in advance if there is a reasonable cause.

The investigator may discontinue the study after giving a written notice to the sponsor at an appropriate timing in advance if there is a reasonable cause.

An advance written notice is not required if the study is discontinued for safety related reasons.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Sponsor or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Sponsor monitors/auditors or its agents and appropriate

regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the study site may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Sponsor, or companies working with or on behalf of Sponsor, and/or to inspection by appropriate regulatory authorities.

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

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Sponsor and should not be made available in any form to third parties, except for authorized representatives of Sponsor or appropriate regulatory authorities, without written permission from Sponsor.

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

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

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigative site as well as at Sponsor and clearly

identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

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

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to Sponsor, such as another investigator, another institution, or an independent third party arranged by Sponsor. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Sponsor.

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

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association [1996 & 2008]).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Sponsor and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by Sponsor in order to de-identify study subjects. The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Sponsor will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

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

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

The investigator must ensure that each study subject or his or her legally acceptable representative, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

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

The investigator or a person designated by the investigator will obtain written informed consent from each subject or his/her guardian, or subject's assent if applicable, before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document/assent document.

12.4. Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Sponsor will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

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

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

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

13. DEFINITION OF END OF TRIAL

Completion of this study is defined as the time of the final observation of the final subject (24 hours after dosing of the investigational product).

14. SPONSOR DISCONTINUATION CRITERIA

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

If a study is prematurely terminated or discontinued, Sponsor will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 1 week. As directed by Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Publications by Sponsor

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

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

www.clinicaltrials.gov

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

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

EudraCT

Sponsor posts EU Basic Results on EudraCT for all Sponsor-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the primary completion date for studies in adult populations or within 6 months of the primary completion date for studies in pediatric populations.

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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

16. REFERENCES

[1] Sakura S, Saito Y. Role of α2 adrenoceptor agonists in clinical anesthesia. Anesthesia 21 Century 2001;3:490-6.

[2] Kamibayashi T, Maze M. Clinical uses of alpha2 -adrenergic agonists. Anesthesiology 2000;93:1345-9.

[3] Bloor BC. General pharmacology of α2-adrenoceptors. Anaesthetic Pharmacology Review 1993:221-32.

[4] Nelson LE, Lu J, Guo T, et al. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology 2003;98:428-36.

[5] Huupponen E, Maksimow A, Lapinlampi P, et al. Electroencephalogram spindle activity during dexmedetomidine sedation and physiological sleep. Acta anaesthesiologica Scandinavica 2008;52:289-94.

[6] Hall JE, Uhrich TD, Barney JA, et al. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesthesia and analgesia 2000;90:699-705.

[7] Aitkenhead AR. Analgesia and sedation in intensive care. British journal of anaesthesia 1989;63:196-206.

[8] Yoshiya I, Nishimura S, Taenaka N. Sedation in Intensive Care Anesthesia 21 Century 2000;2:333-7.

[9] Katsanoulas C. Concluding Remarks: Redefining Intensive Care Unit Sedation. International Congress and Symposium Series 1998;221:83-8.

[10] Mantz J, Singer M. Importance of Patient Orientation and Rousability as Components of Intensive Care Unit Sedation. International Congress and Symposium Series 1998;221:23-9.

[11] Kumon K TS, Hanaoka K, Yoshiya I, Nomura M, Adachi T, et al. Usage of Dexmedetomidine. The Japanese Journal of Respiratory Care 2004;21:29-37.

[12] Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. Critical care 2000;4:302-8.

[13] Hsu YW, Cortinez LI, Robertson KM, et al. Dexmedetomidine pharmacodynamics: part I: crossover comparison of the respiratory effects of

dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology 2004;101:1066-76.

[14] Ebert TJ, Hall JE, Barney JA, et al. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382-94.

[15] Precedex Interview Form (revised in April 2014, revised version 4)

[16] Internal material: Results of a Phase I study on Japanese expatriates living abroad (continuous dosing study)

[17] Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. Jama 2012;307:1151-60.

[18] Guidelines for Drug Therapy in Pediatric Patients with Cardiovascular Diseases (JCS2012), 2012, 213-20.

[19] Guidelines for the Use of Anesthesia and Anesthesia-related Drugs, Version 3, X Pediatric Anesthesia, Japanese Society of Anesthesiologists 2012; 414-5.

[20] Candidate drug therapies (proposed) to be reviewed at the "1st Meeting of Council for Paediatric Pharmacotherapy (held on March 30, 2006); Document 7 "Council for Paediatric Pharmacotherapy"

[21] Diaz SM, Rodarte A, Foley J, et al. Pharmacokinetics of dexmedetomidine in postsurgical pediatric intensive care unit patients: preliminary study. Pediatr Crit Care Med 2007; 8(5): 419-424.

[22] Zuppa AF. The pharmacokinetics and pharmacodynamics of dexmedetomidine in infants following open heart surgery. Society of Critical Care Medicine presentation#23; January 8, 2006

[23] Guidelines for perioperative cardiovascular evaluation and management for noncardiac surgery (revised version 2014)

[24] Haque IU, Zaritsky AL. Analysis of the evidence for the lower limit of systolic and mean arterial pressure in children. Pediatric critical care medicine : a journal of the Society of Critical Care Medicine and the World Federation of Pediatric Intensive and Critical Care Societies 2007;8:138-44.

[25] Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011;377:1011-8.

[26] Kazuya Tachibana, Muneyuki Takeuchi: Dexmedetomidine and Sedation; Methods of Using DEX in Children; Methods of Perioperative Administration and Points to Note [in Japanese]:LiSA 2014; 21(03): 224-8 2014

[27] Precedex™ United States package insert (USPI)

[28] Curley, MA, Harris, SK, Fraser, KA, et al. State Behavioral Scale: A sedation assessment instrument for infants and young children supported on mechanical ventilation. Pediatric Critical Care Medicine, 2006; 7(2): 107-114. (PMID: 16446601)
http://www.marthaaqcurley.com/uploads/8/9/8/6/8986925/sbs_japanese.pdf