Protocol C0801017

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

Statistical Analysis Plan
(SAP)

Version: 4.0

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[redacted]

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APPENDICES

1. VERSION HISTORY

This Statistical Analysis Plan (SAP) for study C0801017 is based on the protocol dated 24 March, 2016.

Table 1. Summary of Major Changes in SAP Amendments

SAP Version	Change	Rationale
1	Not Applicable	Not Applicable
2	Section 4.2: Add [Prohibited concomitant drug before the start of dexmedetomidine administration and after the end of dexmedetomidine administration is outside the scope of the criterion 1].	- Clarify the period of prohibited concomitant drug for per protocol set
	Section 5.2.4: Add [be the last observed time which may represent time of subject's withdrawal from the study, time of the end of the period, time of death, time of the last recorded observation during the period, whichever happened first].	- Add explanations of censoring
	Section 6.2.2: Add a detail analysis method for a case where rescue medication will be used continuously over an analysis time point.	- Add the analysis method in the case of unexpected cases occur
	Section 6.2.4: Add and change [There are two analysis points. One is at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation, whichever is earlier. The other is at the conclusion of mechanical ventilation].	- Add a different analysis point based on rationale of this endpoint - Correct an explanation of previous written analysis point
	Section 6.3.1: Plots of mean concentration-time profile by age group, mean dose-normalized concentration-time profile by age group and individual concentration-time profiles by age group were added. In addition, a list of concentration, actual time points and SBS scores was added.	- Add plots for mean concentration-time profile by age group - Add plots for mean dose-normalized concentration-time profile by age group - Add individual plots for concentration-time profle by age group - Add a list of concentration with actual time points and SBS scores
	Section 6.3.2: Add [In addition, individual SBS scores will be listed].	- Add a list of SBS scores
	Section 6.5: Add [CGA will be listed and only used to evaluate whether a subject's age is equal to or higher than a lower limit of age group 1 described in Section 6.4 when categorizing age. Otherwise age calculated using birthday records will be used for summary of age and evaluation of the age category].	- Add detail descriptions of age for under 1 year old subjects
	Section 6.5:Add [ASA classification will be summarized according to Section 5.2.3 and listed].	- Add a summary and a list of ASA classification

	Section 6.5: Change [Drugs administered druing surgery for anesthesia will be summarized with total dosage given over the time period. -> Prior and concomitant medications will be listed with total dosage].	- A list of prior and concomitant medications which includes drug information for anesthesia during surgery will be generated.
	Section 6.6: Add [(eg, vital signs)].	- Add an example of safety evaluation using major time points
	Section 6.6: Add [Incidence of laboratory test abnormalities will be summarized. All laboratory data, laboratory test abnormalities by subject and laboratory test abnormalities by test will be listed separately].	- Add a burette of laboratory test values and its evaluation details
	Section 6.6: Change [maintenance-> exposure].	- Change a word in summary of exposure to study drug
	Section 6.6: Change [summarized -> listed].	- Change summary to list of adverse event occurred after end of administration of dexmedetomidine for incident of withdroawal symptoms
	Section 6.6: Add [Medication error will be listed].	- Add a list of medication error
	Appendix table 3: Remove [or the last observation, whichever is earlier. (#18)].	- Correct an explanation according to change of corresponding section
	Appendix table 3: Add [The analysis point will be at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation, whichever is earlier. The start point of this evaluation is initiation of administration. (#19)].	- Add an analysis using a different analysis point
	Appendix table 3: Change [#19 -> #20].	- Shift the number one line
3	Section 3.2 Endpoint # 9: Add [and weight adjusted total dose]	- Add based on protocol administrative change letter on December 16, 2016.
	Section 5.2.1: Change descriptions and add 95% confidence interval	- Considering consistency with outputs for the analysis
	Section 5.2.2: Change [quantiles -> quartiles]	- Minor modification to make the derection more correctly
	Section 5.2.4: Delete descriptions regarding subjects at risk.	- It was difficult technically to display subjects at risk on KM-plot.
	Section 6.1.1.1, 6.2.1, 6.2.2, 6.2.3: Add definition for the analysis point for the patients who discontinue the study drug earlier than the previous defined analysis points as an exception	- To deal with unexpected cases in the protocol.
	Section 6.3.2 Add analysis population for the analysis	- Add a missing point
	Section 6.6 Add detailed explanations in the descriptions of continuous variables and categorical	- Described in detail

	variables.	
	Section 6.6 Add analysis for exclusions from primary evaluation	- Add a missing analysis
	Section 6.6 Add a list for administration recodes	- Add a missing analysis
	Section 6.6 Add detailed explanations for the summary of vital signs	- Add a missing analysis
	Section 6.6 Add a list of hospitalization details and detailed explanation of ICU discharge time for the summary	- Add a missing analysis
	Section 6.6 Add a list for the surgery details, fluid volume and gradually reducing of administration rate to complete treatment with dexmedetomidine	- Add a missing analysis
	Section 6.6 Add summary and a list for previous and/or concomitant drug/non-drug	- Add a missing analysis
	Appendix 1, Table 3: Change descriptions according the newly defined analysis points in Section 6.1.1.1, 6.2.1, 6.2.2, 6.2.3	- To deal with unexpected cases in the protocol.
4	Section 5.5: Add a condition for exclusion of analysis	- Applied this for all figures - Add plasma samples may have incomplete or inaccurate sample collection -Change of expression
	Section 6.2.1: Add an additional analysis point of the responder analysis for rescue medications.	- Exploratory analyses
	Section 6.2.3: Add detail explanations for analysis points for calculating evaluated values as endpoint 3,7 and 8	- To make the calculation clear for those endpoints
	Section 6.2.3: Change the analysis time point of endpoint 8	- Correct typo
	Section 6.2.3: Delete a term of “the” in analysis methodology paragraph due to confusing	- To avoid misunderstanding
	Section 6.3.1: Add a descriptive summary of the plasma dexmedetomidine concentrations based on nominal time points by age group	-Add a descriptive summary by age group
	Section 6.4: Delete terms of "Group" described for exposure to study drug and modify categories.	- To avoid misunderstanding - Exposure categories were reviewed and needed to modify.
	Section 6.6: Add a description of all adverse events in addition to TEAE	- Summary of events which occurred both before and after initial administration of a study drug was needed considering with this protocol design.
	Section 6.6: Add evaluation time points for vital signs and name of the time points (major time point) was changed to analysis time point.	- More time points were needed to assess longitudinal transition.
	Section 6.6: Summary was added for Incident of withdrawal symptoms.	- Summary was needed besides to a listing
	Section 6.6: Add descriptions of adverse events of subjects dosed over 24 hours	- Summary was needed for the specific adverse events

	Section 6.6: Add descriptions for the Intubation summary	- Add descriptions how to deal with too long intubation time or not applicable records
	Section 6.6: Add descriptions for the hospitalization summary	- Add descriptions how to deal with too long hospitalization time or not applicable records
	Appendix 1 (Table 3): Add exploratory analyses regarding rescue medications	- Add two rows in correspondence with the exploratory responder analyses

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in study C0801017. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

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

2.2. Study Design

This study is a phase 3, multi-center, single-arm, open-label study evaluating the efficacy, safety, and pharmacokinetics (PK) of dexmedetomidine administered as continuous IV infusion in pediatric subjects aged ≥45 weeks CGA to <17 years old.

In this study, there are two types of cases described in following figures.

Figure 1. Elective Surgical Cases

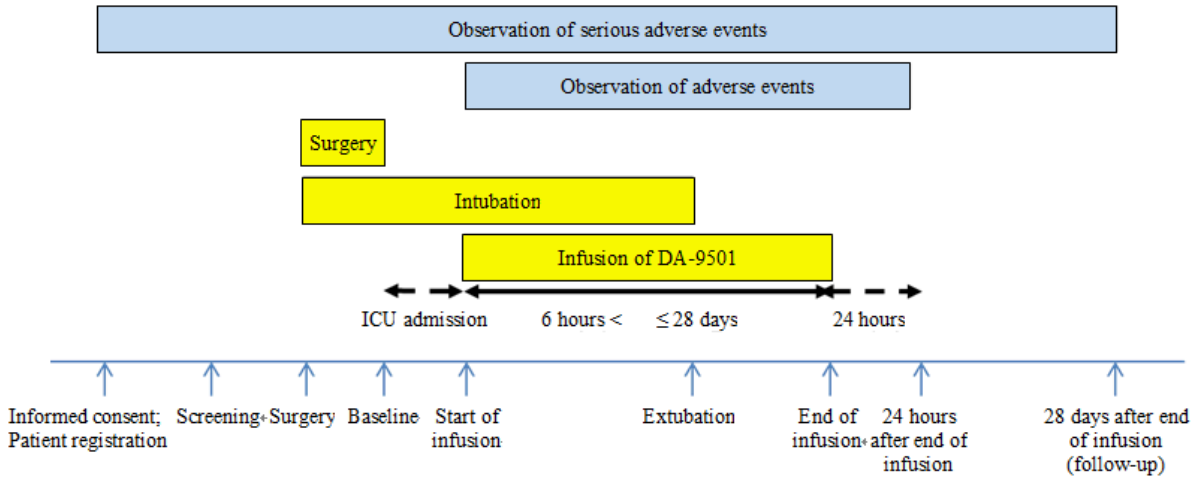
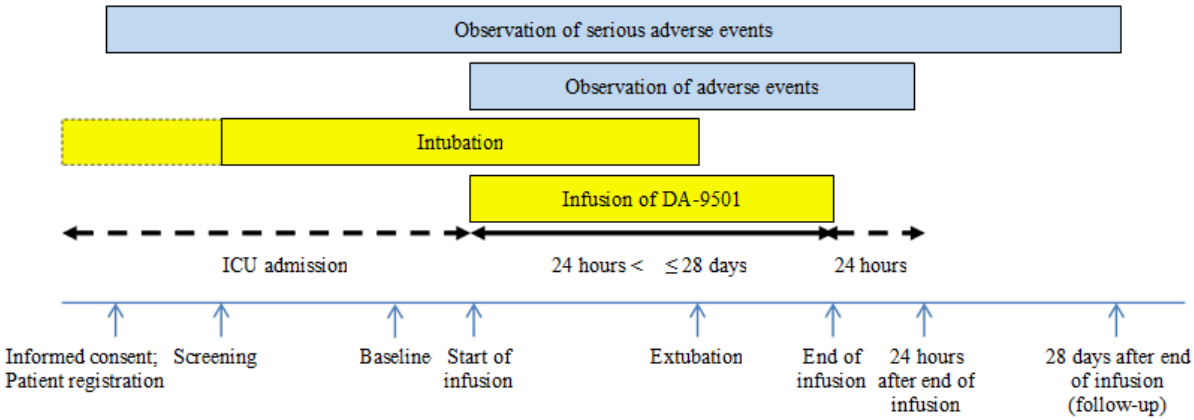


Figure 2. Medical ICU Cases



Target sample size is 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 number of subjects for efficacy/safety evaluation and the target number of subjects for PK evaluation by age group are as follows.

Table 2. Target number of subjects

Age group		Efficacy/safety evaluation: Target number of subjects	Number of subjects for PK evaluation[a]
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

a Of enrolled subjects, those from whom informed consent for blood sampling for PK measurement is obtained

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Percentage of subjects who did not use a rescue sedative (midazolam) during mechanical ventilation to achieve/maintain adequate sedation (efficacy percentage) from the start of dexmedetomidine administration to 24 hours after the initial administration or conclusion of mechanical ventilation. If the mechanical ventilation is concluded within 24 hours of dexmedetomidine administration, the record at conclusion of mechanical ventilation will be used for the primary endpoint.

3.2. Secondary Endpoint(s)

i. From the start of dexmedetomidine administration to 24 hours after the initial administration or conclusion of mechanical ventilation when mechanical ventilation is concluded within 24 hours of dexmedetomidine administration,

   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. Dose level corrected for total dose of rescue sedative/analgesic during mechanical ventilation and for body weight.

   3. Duration and percentage of maintenance of target sedation level during mechanical ventilation.

ii. From 24 hours of dexmedetomidine administration to conclusion of mechanical ventilation when dexmedetomidine administration exceeds 24 hours,

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

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

6. Dose level corrected for total dose of rescue sedative/analgesic during mechanical ventilation and for body weight.

7. Duration and percentage of maintenance of target sedation level during mechanical ventilation.

iii. From after extubation to conclusion of dexmedetomidine administration,

8. Duration and percentage of maintenance of target sedation level after extubation.

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

iv. From the start of dexmedetomidine administration to conclusion of mechanical ventilation,

10. Time until the end of mechanical ventilation.

3.3. PK Endpoints

Plasma dexmedetomidine concentration.

3.4. Baseline Variables

There is no model based on analysis using a baseline value as a variable.

3.5. 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 (abstinence) symptoms (presence/absence of hypertension, tachycardia, or agitation symptoms after the end of dosing of the investigational product).
- Electrocardiogram (ECG).

3.5.1. Adverse Events

AEs (regardless of seriousness) will be recorded in the case report form (CRF) between the time when the subject has taken at least 1 dose of the investigational product and the last visit (24 hours after the end of dosing of the investigational product in the case of this study).

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 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.

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. Other postoperative symptoms are to be reported as AEs.

Changes in laboratory test values that are normally observed in elective surgical cases or medical ICU cases 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.

3.5.2. Baseline values

The baseline assessment is defined as the last assessment recorded before study drug administration. If baseline data is recorded at both screening visit and baseline visit, data at baseline visit will be used as baseline data for the safety endpoint. If baseline data is recorded at either screening visit or baseline visit, the existing data at screening visit or baseline visit will be used as baseline data for the safety endpoint. If baseline data is recorded at neither screening visit nor baseline visit, baseline data for the safety endpoint will be missing. This algorism will be applied to endpoints which are observed at both screening visit and baseline visit.

4. ANALYSIS SETS

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

4.1. Full Analysis Set

The Full Analysis Set (FAS) is composed of all subjects who have received at least one dose of the investigational product. FAS is the primary analysis population for efficacy evaluation.

4.2. Per Protocol Analysis Set

The Efficacy Evaluation analysis set (EE) will be a subset of the FAS dataset and include subjects that satisfy both of the following criteria:

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 receiving study drug excludes interruptions.

Prohibited concomitant drug before the start of dexmedetomidine administration and after the end of dexmedetomidine administration is outside the scope of the criterion 1. The definition of prohibited concomitant drugs is described in Section 5.8.1 "Prohibited Concomitant Drugs" in the protocol amendment 2.

EE is the secondary analysis population for efficacy evaluation.

4.3. Safety Analysis Set

The definition of safety analysis set (SS) is the same as that of FAS. SS is the primary population for safety evaluation.

4.4. PK Analysis Sets

The PK analysis population is defined as all subjects treated with dexmedetomidine over at least 6 hours and measured at least 1 plasma concentration.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The lower limit of 95% confidence interval of primary endpoint described in Section 3.1 will be compared with threshold value (40%) set as an intermediary efficacy rate between the placebo (20%) and dexmedetomidine(60%).

5.2. General Methods

5.2.1. Analyses for Binary Data

Estimation

For a single binominal proportion, 95% confidence interval will be calculated as a two-sided, 2.5% upper and lower intervals, based on Agresti-Coull's method (Agresti and Coull, 1998, Lawrence D. Brown et al, 2001).

Descriptive summary

Following statistics will be used: number of subjects, number of subjects with the response, percentage of the responses and its 95% confindence interval.

5.2.2. Analyses for Continuous Data

Descriptive summary

Following statistics will be used: number of subjects, mean, standard deviation, median, minimum, maximum, and quartiles.

5.2.3. Analyses for Categorical Data

Descriptive summary

Following statistics will be used: number and percentage of subjects in each category.

5.2.4. Analyses for Time to Event Data

Time-to-event endpoints will be summarized using the Kaplan-Meier method and estimated survival curves will be displayed graphically when appropriate. The time of median and quartiles (hours) will be estimated by the Kaplan-Meier method. Confidence interval for median and quartiles are based on the Brookmeyer-Crowley method.

The subjects who did not have the event of interest during the corresponding evaluation period that starts at the time of first study drug infusion will be considered censored. The time of censoring will be the last observed time which may represent time of subject's withdrawal from the study, time of the end of the period, time of death, time of the last recorded observation during the period, whichever happened first.

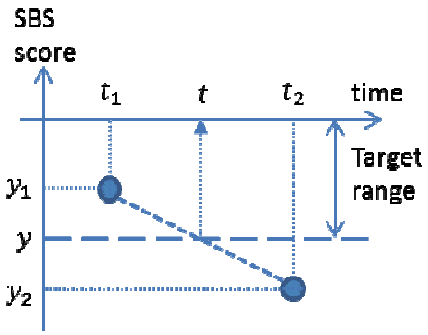
5.2.5. Linear Interpolation

The two coordinates are given as (t_1,y_1) and (t_2,y_2). If y are given in the interval $[y_1, y_2]$, the value t along the straight line between these coordinates is calculated from the following equation;

$$\frac{t - t_1}{y - y_1} = \frac{t_2 - t_1}{y_2 - y_1}$$

An example figure for a linear interpolation in the above situation is as follows:

Figure 3. Example for a Linear Interpolation



5.3. Methods to Manage Missing Data

No imputation rule will be applied to missing data in efficacy evaluation, while a standard algorithm for imputation will be applied to safety evaluation if needed.

5.4. Concentrations below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero.

5.5. Deviations, Missing Concentrations and Anomalous Values

In summary tables, figures (including individual plots), concentration value will be treated as missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie, not done) or NS (ie, no sample);

2. A gap in sampling time between prescribed and actual time is of sufficient concern or a concentration has been flagged anomalous;

3. Plasma samples may have incomplete or inaccurate sample collection.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

6.1.1. Percentage of Subjects who did not Use a Rescue Sedative (midazolam) during Mechanical Ventilation to Achieve/maintain Adequate Sedation (efficacy percentage)

6.1.1.1. Primary Analysis

- Analysis time points**:** The analysis point will be at 24 hours from administration of dexmedetomidine or at the conclusion of mechanical ventilation, whichever is earlier. The start point of this evaluation is initiation of administration. If administration of dexmedetomidine is discontinued earlier than both time points of 24 hours from administration and the conclusion of mechanical ventilation, the analysis point will be at the end of administration of dexmedetomeidine.

- Analysis population**:** FAS.

- Analysis methodology**:** Estimation described in Section 5.2.1.

Reporting results:

- The total number of FAS, the number of subjects with no additional sedative(midazolam), the percentage and its 95% confidence interval will be presented.

6.1.1.2. Sensitivity/Robustness Analyses

The same analysis as the primary analysis will be conducted in EE. The reporting results will be also the same as Section 6.1.1.1.

In addition, total number, the number of subjects with no additional sedative(midazolam) and its percentage in each age group (see Section 6.4) will be reported by FAS and EE according to descriptive summary described in Section 5.2.1.

6.2. Secondary Endpoint(s)

6.2.1. Endpoint for Responder

Responder is defined as a subject who did not require administration of a rescue medication(midazolam/fentanyl) during mechanical ventilation in addition to administration of the investigational product . The endpoints for responder are 1, 4 and 5 described at Section 3.2.

- Analysis time points**:** If the endpoint is 1, the analysis point will be at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation, whichever is earlier. The start point of this evaluation is initiation of administration of dexmedetomidine. If the endpoint is 4 or 5, the analysis point will be at the conclusion of mechanical ventilation. The start point of this evaluation is at 24 hours after initial administration of dexmedetomidine. If administration of dexmedetomidine is discontinued earlier than both time points of 24 hours from administration and the conclusion of mechanical ventilation for the endpoint 1 or than the conclusion of mechanical ventilation for the endpoints of 4 and 5, the analysis point will be at the end of administration of dexmedetomeidine.

- Analysis population**:** FAS, EE.

- Analysis methodology**:** Descriptive summary described in Section 5.2.1.

Reporting results:

- All calculated descriptive summaries based on Section 5.2.1 for each endpoint will be reported.

- In addition, the percentage of subjects who did not use a rescue medication (midazolam/fentanyl) will be calculated during the period from after extubation to conclusion of dexmedetomidine administration as exploratory analyses in the same manner as above.

6.2.2. Endpoint for Dosage

The endpoints for dosage are 2, 6 and 9 described at Section 3.2.

- Analysis time points**:** If the endpoint is 2, the analysis point will be at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation, whichever is earlier. The start point of this evaluation is initiation of administration. If the endpoint is 6, the analysis point will be at the conclusion of mechanical ventilation. The start point of this evaluation is at 24 hours after initial administration of dexmedetomidine. If administration of dexmedetomidine is discontinued earlier than both time points of 24 hours from administration and the conclusion of mechanical ventilation for the endpoint 2 or than the conclusion of mechanical ventilation for the endpoint 6, the analysis point will be at the end of administration of dexmedetomeidine. If the endpoint is 9, the analysis point will be at the conclusion of mechanical ventilation. The start point of this evaluation is at the point of extubation.

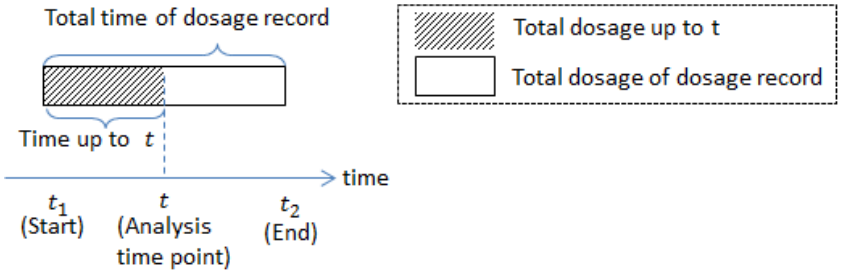
- Analysis population**:** FAS, EE.

- Analysis methodology**:** Descriptive summaries described in Section 5.2.2 for total dosage and dosage compensation based on weight of rescue medication will be calculated separately for only rescued subjects and all subjects by each rescue medication (midazolam/ fentanyl). In this analysis, the rescued subject is defined as a subject who received any amount of rescue medication in the target evaluation period for each endpoint. The dose of the subjects who did not receive rescue medication will be treated as zero in the calculation for the descriptive summaries of all subjects.

If rescue medication is used continuously over the analysis time point (Figure 4 shows an example case), total dosage up to the analysis time point will be calculated as follows:

Figure 4. Rescue Medication Dosage Record

$$\text{total dosage of the dosage record} \times \frac{\text{time up to the analysis time point } (t-t_1)}{\text{total time of the dosage record } (t_2-t_1)}$$



Reporting results:

- The summary tables will be generated by the type of the endpoints (total dosage/weight adjusted dosage), the type of the subjects (rescued/all), and the type of the rescue medication(midazolam/fentanyl) according to Section 5.2.2, respectively.

6.2.3. Endpoint for Maintenance Time of Target Sedation

The endpoints for maintenance time of target sedation are 3, 7 and 8 described at Section 3.2.

- Time that the target sedation is maintained/achieved.

  The target sedation scores by state behavioral scale (SBS) are −2 to 0 while intubated and −1 to 0 after extubation (See table 5 in the protocol amendment 2 for the details). If the subjects meet the target sedation score at the analysis point for the evaluation period, the subjects will be regarded as maintain/achieve target sedation.

  If one of the consecutive SBS scores is out of the target range (-2 to 0 while intubated/-1 to 0 after extubation), a linear interpolation described in Section 5.2.5 will be used between them to estimate the time within the SBS target range and above or below the range. If there are several SBS scores at one time, then the average of these scores will be used. Then the absolute time that the subject in the SBS target range will be calculated for each subject as the total amount of time where the estimated SBS scores are in the SBS target range. The percentage of the time will be derived then as a ratio of the time in SBS target range while the evaluation period for the endpoint.

  - Analysis time points**:** If the endpoint is 3, the analysis point will be at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation, whichever is earlier. The start point of this evaluation is initiation of administration. If the endpoint is 7, the analysis point will be at the conclusion of mechanical ventilation. The start point of this evaluation is at 24 hours after initial administration of dexmedetomidine. If the analysis point is at the conclusion of mechanical ventilation, values measured at designated allowance intervals of before extubation visit will be used for both numerator and denominator in endpoint 3 and 7. In addition, if administration of dexmedetomidine is discontinued earlier than both time points of 24 hours from administration and the conclusion of mechanical ventilation for the endpoint 3 or than the conclusion of mechanical ventilation for the endpoint 7, the analysis point will be at the end of administration of dexmedetomeidine. If the endpoint is 8, the analysis point will be the end of administration of dexmedetomidine. Evaluated duration will be the same between numerator and denominator. The start point of this evaluation is at the point of extubation.

  - Analysis population**:** FAS, EE.

  - Analysis methodology**:** Number of subjects that spent any amount of time in SBS target range and its percentage will be summarized according to Section 5.2.1.

Descriptive summaries for absolute time in hours and its percentage regarding the maintained interval of the target sedation will be calculated according to Section 5.2.2. In the same table, total absolute time in hours of the analysis population will be also summarized according to Section 5.2.2.

As a sensitivity analysis, the endpoint 3 will be also analysed using an analysis point which is the earliest point among 24 hours after initial administration of dexmedetomidine, the conclusion of mechanical ventilation, the end of administration of dexmedetomidine and initiation of gradually reducing of administration rate to complete treatment with dexmedetomidine. The start point of this evaluation is initiation of administration.

Reporting results:

- All calculated descriptive summaries based on Section 5.2.1 and Section 5.2.2 for each endpoint will be reported.

6.2.4. Endpoint of Time to Event

The endpoint of time to event is the endpoint 10 described at Section 3.2. The event in this analysis is conclusion of mechanical ventilation.

- Analysis time points**:** There are two analysis points. One is at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation, whichever is earlier. The other is at the conclusion of mechanical ventilation. The start point of this evaluation is initiation of administration.

- Analysis population**:** FAS, EE.

- Analysis methodology**:** Descriptive summary and figures described in Section 5.2.4 will be generated.

The same analysis without figures will be also conducted by age group.

6.3. Other Endpoint(s)

6.3.1. PK Endpoints

The following reporting of PK data will be done:

- A descriptive summary of the plasma dexmedetomidine concentrations based on nominal time points.

- A descriptive summary of the plasma dexmedetomidine concentrations based on nominal time points by age group.

- Plots of mean plasma dexmedetomidine concentrations against nominal time post dose (on both linear and semi-log scales) by age group in one graph for all age group.

- A descriptive summary of the plasma dexmedetomidine concentrations based on nominal time points by age group and presence or absence of taper.
- Plots of mean plasma dexmedetomidine concentrations against nominal time points (on both linear and semi-log scales) by age group and presence or absence of taper in one graph for all age groups.
- A descriptive summary of the plasma dexmedetomidine concentrations based on nominal time points by age group, presence or absence of taper and presence or absence of additional sedative (midazolam).
- Plots of mean plasma dexmedetomidine concentrations against nominal time post dose by age group, presence or absence of taper and presence or absence of additional sedative (midazolam) in one graph for same combination of age group and taper condition.
- A descriptive summary of the dose-normalized plasma dexmedetomidine concentrations based on nominal time points.
- Plots of mean dose-normalized plasma dexmedetomidine concentrations against nominal time post dose (on both linear and semi-log scales) by age group in one graph for all age group.
- A descriptive summary of the dose-normalized plasma dexmedetomidine concentrations based on nominal time points by age group and presence or absence of taper.
- Plots of mean dose-normalized plasma dexmedetomidine concentrations against nominal time points (on both linear and semi-log scales) by age group and presence or absence of taper in one graph for all age groups.
- Box plots of plasma dexmedetomidine concentrations at 1-2 hours before the end of dosing or before the start of tapering represented by age group.
- Box plots of plasma dexmedetomidine concentrations at 1-2 hours before the end of dosing or before the start of tapering represented by age group and presence or absence of additional sedative (midazolam) in one graph for each age group.
- A listing of all plasma dexmedetomidine concentrations sorted by subject, age group and nominal time points. The listing of concentrations will also include the actual time points.
- Individual plots of plasma dexmedetomidine concentrations against actual time post dose (on both linear and semi-log scales) represented by age group.
- Individual plots of plasma dexmedetomidine concentrations against actual time points (on both linear and semi-log scales) represented by age group and presence or absence of taper.

- A listing of all plasma dexmedetomidine concentrations sorted by subject, age group and nominal time points. The listing of concentrations will also include the actual time points and SBS scores. SBS scores at closest time points to each blood collection time will be used.
- Individual plots for SBS scores versus the dexmedetomidine plasma concentration at the time to end of dosing by age group in one graph for all subjects. SBS scores at closest time points to each blood collection time will be used.
- Individual plots for SBS scores versus the dexmedetomidine plasma concentration at the time from end of dosing to last PK sample by age group in one graph for all subjects. SBS scores at closest time points to each blood collection time will be used.

The set of statistics will include n, geometric mean, arithmetric mean, median, standard deviation, cv, geometric cv, minimum, maximum and the number of concentrations above the lower limit of quantification.

6.3.2. Longitudinal SBS Score

- Longitudinal individual plots of all recorded SBS scores will be generated by subjects. These plots include information of initiation and conclusion time points about both dexmedetomidine administration and intubation. These figures will be reviewed by internal review committee. In addition, individual SBS scores will be listed. Analysis population of these analyses will be FAS.

6.4. Subset Analyses

For safety and efficacy analyses

Subset analyses regarding age group will be conducted for all efficacy and safety analyses unless otherwise specified.

Age group is defined as follows:

Age group	
I	≥45 weeks CGA, <12 months
II	≥12 months, <24 months
III	≥2 years, <6 years
IV	≥6 years, <17 years

Patient type (Elective surgery or Medical ICU) can be specified with records of surgery and ASA classification. If patient type is Elective surgery, the patient has records of surgery details and ASA classification.

If number of patients in one of patient types is more than 20 subjects, following subgroup analyses will be conducted: For efficacy evaluation, endpoints which are the same definition of a primary endpoint described in Section 3.1 and secondary endpoints of 1, 2 and 3

described in Section 3.2 will be analyzed using FAS by patient type. For safety evaluation, frequency of adverse events will be summarized with severity by patient types.

Exposure to study drug

Exposure to study drug will be summarized by subgroups of time of exposure to the study drug defined as follows:

- Exposure time <6 hours.
- Exposure time >= 6 hours.
- Exposure time > 12 hours.
- Exposure time > 24 hours.
- 6 =< Exposure time <=12 hours.
- 12 < Exposure time <=24 hours.

6.5. Summaries for Baseline Characteristics

The analyses regarding baseline characteristics will be conducted according to Pfizer data standard (PDS) by FAS and EE for both total subjects and each age group unless otherwise specified.

The summary which may be non-PDS is described as follows:

Summary for demography: Age will be summarized with both units of years and months as a continuous variable. Also age will be treated as a category variable described in Section 6.4 for the summary of total subjects. CGA will be listed and only used to evaluate whether a subject's age is equal to or higher than a lower limit of age group 1 described in Section 6.4 when categorizing age. Otherwise age calculated using birthday records will be used for summary of age and evaluation of the age category. Body mass index will not be calculated and summarized. Weight will be summarized as a continuous variable. Patient types (Elective surgery or Medical ICU) will be summarized according to Section 5.2.3. ASA classification will be summarized according to Section 5.2.3 and listed.

List for prior and concomitant medications: Prior and concomitant medications will be listed with total dosage.

6.6. Safety Summaries and Analyses

All safety analyses will be conducted according to PDS by both total subjects and each age group in SS unless otherwise specified.

Adverse events will be summarized by treatement emergent adverse events and all adverse events recorded in CRF, respectively.

Following analysis time points will be used for longitudinal summaries for safety evaluation of vital signs; Baseline (Day1/Pre-dose), Day 1 visits (Day 1/10 minutes, Day 1/20 minutes, …, Day 1/24 hours), End of mechanical ventilation (Extubation/-5 minutes, Extubation/5

minutes), End of dosing (End of treatment/0 minute), 24 hours after end of dosing (End of treatment/24 hours), Visits for rescue medications (Rescue Medications [Fentanyl or Midazolam]/-5 minutes, Rescue Medications [Fentanyl or Midazolam]/5 minutes), Unplanned visits (Change Infusion rate/-5 minutes, Change Infusion Rate/5 minutes) and Discontinuation. Subjects may be duplicated in the summaries of Visits for rescue medications and Unplanned visits. Continuous variables of vital signs will be summarized for actual values and change from baseline by descriptive statistics at each analysis time point.

Categorical variables for ECG at each analysis time point [Baseline (Day1/Pre-dose), 24 hours after initial dosing(Day1/24H), End of mechanical ventilation (Extubation/5MIN), End of dosing(End of treatment/0MIN) and 24 hours after end of dosing (End of treatment/24H)] will be summarized by number and its percentage. In addition, change from baseline of them will be summarized by cross table. For evaluation of 24 hours after end of dosing (End of treatment/24H), only subjects who complete the study treatment will be summarized.

In terms of fluctuation, the following variables are of interest in particular:

1. Vital signs (Systolic Blood Pressure[SBP], Diastolic Blood Pressure [DBP], Heart Rate[HR], Respiratory Rate[RR]), Oxygen Saturation of Arterial Blood [SpO_2], End Tidal CO_2[$ETCO_2$], core body temperature, and body weight.

2. Laboratory test values.

The following may be study-specific summaries:

- Exclusions from primary evaluation

  The number of subjects in per protocol set out of full analysis set and it's percentage will be calculated.

- Summary of exposure to study drug

  Total exposure dose, average exposure dose and total esposure time of the study drug will be summarized in the same table. The subgroup analysis using exposure time group will be also conducted in the same manner, respectively. In addition, administration recodes including variables used in summary of exposure to study drug will be listed.

- Vital sign

  Actual values and change from baseline of vital signs, SpO_2, $ETCO_2$ and body weight will be summarized by descriptive statistics at each analysis time point. In terms of records for 24 hours after end of dosing (End of treatment/24H), summaries will be made separately for subjects who completed the study treatment as "End of treatment/24H" and subjects who experienced early discontinuation before the study treatment completion as "Discontinulation".

Longitudinal records for vital signs, SpO_2,ETCO2 and body weight with information of subject ID, administration rate(μg/kg/hour) and actual time will be generated as a list format.

- Laboratory test values

  Incidence of laboratory test abnormalities will be summarized. All laboratory data, laboratory test abnormalities by subject and laboratory test abnormalities by test will be listed separately.

- Incident of withdrawal symptoms

  Adverse event occurred after end of administration of dexmedetomidine will be summarized and listed in order to evaluate occurrence of withdrawal (abstinence) symptoms (eg, presence/absence of hypertension, tachycardia, or agitation symptoms after the end of dosing of the investigational product).

- Adverse events of subjects dosed over 24 hours

  Incidence of adverse events (all causality, treatment related) occurred after 24 hours of dosing will be summarized for subjects dosed over 24 hours by severity, respectively.

- Intubation details

  Duration (hour) of intubation will be summarized according to Section 5.2.2. If time of extubation is over 24 hours after the end of dosing in subjects who completed the study, time of 24 hours after the end of dosing will be used in the summary. In addition, time of end of dosing will be used in the summary if extubation time is later than the end of dosing or not reported for subjects who discontinued from the study. In addition, reasons for intubation will be summarized according to Section 5.2.3. Other reasons recorded by text descriptions will be summarized as a list format separately.

- Ventilator settings

  Records of ventilator setting will be summarized as a list format.

- Hospitalization details

  Duration from ICU admission to ICU discharge will be summarized according to Section 5.2.2 and listed. If ICU discharge time is over 24 hours after the last administration, it is regarded as 24 hours after the last administration in the summary. In addition, time of end of dosing will be used in the summary if discharge time is later than the end of dosing or not reported for subjects who discontinued from the study.

- Surgery details

  Duration of surgery will be summarized according to Section 5.2.2. Data used in the summary will be also listed.

- Fluid Volume

  Total input and output fluid volume will be summarized separately according to Section 5.2.2. Data used in the summary will be also listed.

- Gradually reducing of administration rate to complete treatment with dexmedetomidine

  Number of patients who experienced gradually reducing of administration rate to complete treatment with dexmedetomidine and its percentage will be summarized according to Section 5.2.3. Data used in the summary will be also listed.

- Medication error

  Medication error will be listed.

- Previous and/or concomitant drug/non-drug

  Previous and concomitant drug/nondrug will be summarized by number of subject for each drug/nondrug and listed. In addition, concomitant rescue medications (Midazolam and Fentanyl) will be listed respectively.

7. INTERIM ANALYSES/INTERNAL REVIEW COMMITTEE

Interim analyses for internal review committee (IRC) will be conducted from the view of safety monitoring. The committee meetings will be scheduled when all data of 24 hours after end of administration are available on the first 10 and 20 subjects for the first and second meetings. After the second meeting, additional meetings may be conducted if needed. The detailed procedures of IRC will be documented in internal review committee charter.

8. REFERENCES

1. Agresti, A., and Coull, B.A. (1998). Approximate is better than ‘exact’ for interval estimation of binomial proportions. The American Statistician 52, 119-126.

2. Lawrence D. Brown, T. Tony Cai, and Anirban DasGupta (2001). Interval Estimation for a Binomial Proportion. Statistical Science 16(2), 101-133.

APPENDICES

Appendix 1. SUMMARY OF EFFICACY ANALYSES

Table 3. Summary of Efficacy Analyses

#	Description of Endpoint	Analysis Time Point	End point #	Summary	Analysis Set	Analysis Section #	Reporting Results	Subset	Primary/ Secondary
1	Percentage of subjects who did not use a rescue sedative (midazolam) during mechanical ventilation to achieve/maintain adequate sedation (efficacy percentage)	The analysis point will be at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation or the end of administration of dexmedetomidine, whichever is earliest. The start point of this evaluation is initiation of administration.	§ 3.1	95% confidence interval will be calculated as a two-sided, 2.5% upper and lower intervals, based on Agresti-Coull's method	FAS	§ 6.1.1.1	Total number, the number of subjects with no additional sedative (midazolam), the percentage and its 95% confidence interval	-	Primary
2					EE	§ 6.1.1.2			Sensitivity analysis for primary analysis
3				Descriptive summary	FAS/EE	§ 6.1.1.2, § 6.4	§ 5.2.1	by age group	Secondary
4					FAS			by patient type	Secondary
5		The analysis point will be at the conclusion of mechanical ventilation or the end of administration of dexmedetomidine, whichever is earlier. The start point of this evaluation is at 24 hours after initial administration.	4 in § 3.2	Descriptive summary	FAS/EE	§ 6.2.1, § 6.4	§ 5.2.1	In addition to whole population, subgroup analysis for each age group will be conducted.	Secondary
-		The analysis point will be at the end of administration of dexmedetomidine. The start point is at the conclusion of mechanical ventilation.	-	Descriptive summary	FAS/EE		§ 5.2.1		Exploratory

#	Description of Endpoint	Analysis Time Point	End point #	Summary	Analysis Set	Analysis Section #	Reporting Results	Subset	Primary/ Secondary
6	Percentage of subjects who did not require administration of a rescue analgesic (fentanyl) during mechanical ventilation in addition to administration of the investigational product.	The analysis point will be at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation or the end of administration of dexmedetomidine, whichever is earliest. The start point of this evaluation is initiation of administration.	1 in § 3.2	Descriptive summary	FAS/EE		§ 5.2.1	In addition to whole population, subgroup analysis for each age group will be conducted.	Secondary
7					FAS			by patient type	Secondary
8		The analysis point will be at the conclusion of mechanical ventilation or the end of administration of dexmedetomidine, whichever is earlier. The start point of this evaluation is at 24 hours after initial administration.	5 in § 3.2	Descriptive summary	FAS/EE		§ 5.2.1	In addition to whole population, subgroup analysis for each age group will be conducted.	Secondary
-		The analysis point will be at the end of administration of dexmedetomidine. The start point is at the conclusion of mechanical ventilation.	-	Descriptive summary	FAS/EE		§ 5.2.1		Exploratory
9	Dose level corrected for total dose of rescue sedative/analgesic during mechanical	The analysis point will be at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation or the end of administration of	2 in § 3.2	Descriptive summaries of both total dosage and weight adjusted dosage by each rescue	FAS/EE	§ 6.2.2, § 6.4	§ 5.2.2	In addition to whole population, subgroup analysis for each age group will be conducted.	Secondary

#	Description of Endpoint	Analysis Time Point	End point #	Summary	Analysis Set	Analysis Section #	Reporting Results	Subset	Primary/ Secondary
10	ventilation and for body weight	dexmedetomidine, whichever is earliest. The start point of this evaluation is initiation of administration.		medication(midazolam/ fentanyl) for rescued subjects and all subjects, respectively	FAS			by patient type	Secondary
11		The analysis point will be at the conclusion of mechanical ventilation or the end of administration of dexmedetomidine, whichever is earlier. The start point of this evaluation is at 24 hours after initial administration of dexmedetomidine.	6 in § 3.2		FAS/EE		§ 5.2.2	In addition to whole population, subgroup analysis for each age group will be conducted.	Secondary
12		The analysis point will be at the conclusion of mechanical ventilation. The start point of this evaluation is at the point of extubation.	9 in § 3.2		FAS/EE		§ 5.2.2	In addition to whole population, subgroup analysis for each age group will be conducted.	Secondary
13	Duration and percentage of maintenance of target sedation level during mechanical ventilation	The analysis point will be at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation or the end of administration of dexmedetomidine, whichever is earliest. The start point of this evaluation is initiation of administration.	3 in § 3.2	Descriptive summary	FAS/EE	§ 6.2.3, § 6.4	§ 5.2.1 for percentage. § 5.2.2 for absolute time (sedation time and total observation time)	In addition to whole population, subgroup analysis for each age group will be conducted.	Secondary
14					FAS			by patient type	Secondary

#	Description of Endpoint	Analysis Time Point	End point #	Summary	Analysis Set	Analysis Section #	Reporting Results	Subset	Primary/ Secondary
15		The analysis point will be the earliest point among 24 hours after initial administration of dexmedetomidine, the conclusion of mechanical ventilation, the end of administration of dexmedetomidine and initiation of gradually reducing of administration rate to complete treatment with dexmedetomidine . The start point of this evaluation is initiation of administration.		Descriptive summary	FAS/EE		§ 5.2.1 for percentage. § 5.2.2 for absolute time(sedation time and total observation time)	In addition to whole population, subgroup analysis for each age group will be conducted.	Sensitivity analysis for secondary analysis
16		The analysis point will be at the conclusion of mechanical ventilation or the end of administration of dexmedetomidine, whichever is earlier. The start point of this evaluation is at 24 hours after initial administration.	7 in § 3.2	Descriptive summary	FAS/EE		§ 5.2.1 for percentage. § 5.2.2 for absolute time(sedation time and total observation time)	In addition to whole population, subgroup analysis for each age group will be conducted.	Secondary
17		The analysis point will be at the conclusion of mechanical ventilation. The start point of this evaluation is at the point of extubation.	8 in § 3.2	Descriptive summary	FAS/EE		§ 5.2.1 for percentage. § 5.2.2 for absolute time(sedation time and total observation time)	In addition to whole population, subgroup analysis for each age group will be conducted.	Secondary

#	Description of Endpoint	Analysis Time Point	End point #	Summary	Analysis Set	Analysis Section #	Reporting Results	Subset	Primary/ Secondary
18	Time until the end of mechanical ventilation	The analysis point will be at the conclusion of mechanical ventilation. The start point of this evaluation is initiation of administration.	10 in § 3.2	Descriptive summary, Figure	FAS/EE	§ 6.2.4, § 6.4	§ 5.2.4	In addition to whole population, subgroup analysis for each age group will be conducted except for figures.	Secondary
19		The analysis point will be at 24 hours after initial administration of dexmedetomidine or at the conclusion of mechanical ventilation, whichever is earlier. The start point of this evaluation is initiation of administration.							
20	Longitudinal SBS score	whole study period	-	Figure	FAS	§ 6.3.2	§ 6.3.2	-	Other

Appendix 2. DATA DERIVATION DETAILS

Appendix 2.1. Definition of Protocol Deviations that Relate to Statistical Analyses/Populations

If prohibited concomitant drugs are administrated, it will be impact on analysis population (See Section 4.2). The details are described in Section 5.8.1 “Prohibited Concomitant Drugs” of the protocol amendment 2.