Non-Interventional Study Protocol

C0801023

Precedex® Intravenous Solution Special Investigation (in pediatric patients)

Statistical Analysis Plan

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1. REVISION HISTORY

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
4.0 29-Aug-2022 PPD Final Study Data Set Release	5.4. Subgroups Changed the position of "complication" and "primary disease" so that they are included in the safety analysis instead of the effectiveness analysis. (This represents a correction of typos and there is no influence on analysis sets or analysis content.) Made other editorial revisions.
3.0 19-Jul-2022 PPD 100% DCF Resolution	5.3. Other Analysis Sets Added the Informed Consent Completed Set – Safety (ICCS-S) and Informed Consent Completed Set – Effectiveness (ICCS-E). 5.4. Subgroups Updated the factors considered in the subgroup analysis of effectiveness to include complication and primary disease. 8.2. Statistical Analyses Stated that analyses will also be performed using the ICCS (ICCS-S or ICCS-E). 8.2.1.1. Summarization of participating sites and patients by type of site Deleted the section. 8.2.1.2. Constitution of patients Included the set of patients with informed consent as an analysis set. 8.2.3.1.1. All adverse reactions Updated the plan to include analyses of the duration of treatment to the first onset and the accumulated dose. Added an analysis by age. 8.2.3.1.2. Serious adverse reactions Updated the plan to include analyses of the duration of treatment to the first onset and the accumulated dose. 8.2.3.2.1. All adverse events Added an analysis by age. 8.2.3.2.2. Serious adverse events

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
	Updated the plan to include analyses of the duration of treatment to the first onset and the accumulated dose. 8.2.3.4. Subgroup analyses Added the subgroups by concomitant drug (midazolam, fentanyl, morphine, or other). 9. LISTINGS Specified the sets of patients used. Made other editorial revisions.
2.0 12-Jan-2021 PPD Ongoing	8.2.2.2. Dosing status of Precedex Updated the plan to include a summarization regarding the dilute concentration. 8.2.3.1.3. Details of adverse reactions Modified the categorization of the action taken for the treatment with Precedex to align with the categorization in the integrated dataset. Made other editorial revisions.
1.0 27-Jun-2019 PPD Before Enrollment	First version

2. INTRODUCTION

This document describes the statistical analysis plan for the Precedex® Intravenous Solution Special Investigation (in pediatric patients). In this Statistical Analysis Plan (SAP), citations from the corresponding protocol are indicated in *italics*. This SAP concerns the analyses of combined data from the Special Investigation conducted by Pfizer R&D Japan G.K. and Maruishi Pharmaceutical Co., Ltd..

2.1. Study Design

This is a multicenter cohort study to be conducted in patients treated with this drug. The case report form (CRF) will be filled out based on medical records in which data obtained in actual medical practice are described.

The target sample size is: *100 patients as the safety analysis set (SAS) (Maruishi Pharmaceutical Co., Ltd. and Pfizer Japan Inc. will collect 50 patients each.)*

2.2. Study Objective

To assess the data, including safety profile, of this drug administered for "sedation during and after mechanical ventilation in the intensive care setting" in pediatric patients under actual medical practice.

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses will be conducted for the purpose of periodic safety reporting. Among the analysis items defined in this SAP, only selected items necessary for periodic safety reporting will be analyzed in each interim analysis. A final analysis will be conducted to support application of re-examination. For the final analysis, the full items defined in this SAP will be analyzed.

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5. ANALYSIS POPULATIONS

5.1. Safety Analysis Set

The SAS consists of a full analysis set (FAS) that is as closer as possible to all patients who received this drug.

Specifically, the SAS consists of all registered or reported patients except those who meet any of the following conditions:

1. No CRF has been collected. (Indicated as “CRF not collected” in the study report.)
2. Any violation or deficiency was found regarding the study contract. (Indicated as “Contract violation/deficiency” in the study report.)
3. The registration does not meet all the requirements. (Indicated as “Invalid registration” in the study report.)
4. No administration of this product has been reported. (Indicated as “No treatment information” in the study report.)
5. No information has been reported for adverse events (AEs). (Indicated as “No AE information – No record” in the study report.)

Details of each condition should follow the Guidance for Adoption/Rejection Criteria for Analysis Populations and Handling of Data in Drug Use Investigations.

5.2. Effectiveness Analysis Set

The effectiveness analysis set (EAS) consists of all patients in the SAS except those who meet any of the following conditions:

1. No effectiveness assessment has been reported (Indicated as “No effectiveness information” in the study report.)
2. The drug was administered for an out-of-scope indication (Indicated as “Out-of-scope indication” in the study report.)
3. The duration of treatment or total dose is inadequate (Indicated as “Inadequate treatment” in the study report.)

5.3. Other Analysis Sets

5.3.1. Informed Consent Completed Set – Safety (ICCS-S)

The ICCS-S consists of the patients in the SAS who have provided informed consent about the dissemination and publication of study results.

5.3.2. Informed Consent Completed Set – Effectiveness (ICCS-E)

The ICCS-E consists of the patients in the EAS who have provided informed consent about the dissemination and publication of study results.

5.4. Subgroups

Subgroup analyses of safety will be performed regarding the following patient characteristics:

- Hepatic function disorder [absent, present]
- Renal impairment [absent, present]
- Age 1 [≥45 weeks of corrected gestational age to <6 years of age, ≥6 to <18 years]
- Age 2 [newborn (≤27 days from birth), non-newborn (≥28 days from birth)]

Note: The conditions for retrieving patients with hepatic function disorder/renal impairment are defined in Appendix 2.

Subgroup analyses of safety will also be performed regarding the following factors:

- Concomitant use of another sedative or analgesic [absent, present]
- Duration of treatment 1 [≤24 hours, >24 hours]
- Duration of treatment 2 [≤72 hours, >72 hours]
- Surgery [absent, present]
- Operative procedure [no surgery, cardiovascular, neurosurgery, abdominal, other]

- Clinical department [(pediatric) intensive care/anesthesiology, (pediatric) cardiovascular surgery, (pediatric) neurosurgery, (pediatric) surgery (except cardiovascular surgery and neurosurgery), internal medicine/pediatrics, other]
- Use of heart-lung machine [absent, present]
- Complication [by System Organ Class (SOC)] [absent, present or present for each SOC]
- Primary disease [by SOC] [absent for each SOC, present for each SOC]

Subgroup analyses of effectiveness will be performed regarding the following patient characteristics:

- Age 2 [newborn (≤27 days from birth), non-newborn (≥28 days from birth)]
- Operative procedure [no surgery, cardiovascular, neurosurgery, abdominal, other]
- Clinical department [(pediatric) intensive care/anesthesiology, (pediatric) cardiovascular surgery, (pediatric) neurosurgery, (pediatric) surgery (except cardiovascular surgery and neurosurgery), internal medicine/pediatrics, other]
- Use of heart-lung machine [absent, present]

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse reactions: AEs considered by the physician as treatment-related
- AEs: All-causality AEs
- Serious adverse events (SAEs) or serious adverse reactions: AEs or adverse reactions considered by the physician as serious
- Safety specification:
    - *Important Identified Risks: bradycardia, hypotension, hypertension, hyperglycaemia, withdrawal syndrome, and respiratory depression*
    - *Important Potential Risks: atrioventricular block, cardiac arrest, convulsions, cortisol suppression, hypothermia, ischaemic heart disease, and tachypnoeic potential*
    - *Important Missing Information: safety of concomitant use of other sedatives and analgesics in pediatric patients, safety of use for over 24 hours in pediatric patients, and safety by type of surgical procedure and type of clinical department in pediatric patients*

  The definition of each event should follow the definition in the RMP as of the database release (or the deadline for each reporting).

6.2. Effectiveness Endpoints

- Overall effectiveness assessment: Overall effectiveness of this drug assessed at the end of the treatment with this drug (effective, not effective, indeterminate)

6.3. Other Endpoints

Not applicable.

6.4. Covariates

No covariates or potential covariates have been identified for the safety or effectiveness of this drug from currently available data including those from clinical studies.

7. HANDLING OF MISSING DATA

If the seriousness of an AE, action taken for an AE, or outcome of an AE is missing, they will be treated as having a value of "unknown" when data are summarized. If the causality of an AE is missing, the event will be treated as "treatment-related" when data are summarized.

Cleaning-uncompleted data will be in principle handled as follows:

- Items for which data are missing: For both purposes of summarization and listing, the corresponding data will be treated as missing data (or as "unknown" if they are a categorical variable).
- Items for which data are inconsistent: For both purposes of summarization and listing, the inconsistent data will be treated as missing data. A list of how each set of inconsistent data have been handled will be presented separately.
- No signature: For both purposes of summarization and listing, any record in a CRF with no signature of a contract physician (including when the CRF is signed only by individuals other than contract physicians) will be treated as missing data. For paper CRFs, if the date of signature is missing in spite of an entry field for it, or if the date filled in has an inconsistency (e.g., a date before the start of treatment, or a future date), the corresponding record in the CRF will be regarded as having no signature.

8. STATISTICAL METHODS AND ANALYSES

8.1. Statistical Methods

8.1.1. Continuous Variables

For continuous variables, summary statistics (n, mean, standard deviation [SD], median, maximum, minimum) will be presented.

8.1.2. Categorical Variables

For categorical variables, patients (or another kind of relevant elements) included in each category will be summarized in terms of n and proportion.

8.1.3. Binary Variables

For binary variables, patients included in each binary category will be summarized in terms of n and proportion. The two-sided 95% confidence interval (CI) will be determined using an exact method if a CI should be determined for the proportion.

When comparisons of the proportion should be made between subgroups, their risk ratio (RR) will be presented with the 95% CI (See Appendix 1).

8.2. Statistical analyses

Unless otherwise stated, analyses performed using the SAS will also be performed using the ICCS-S. Similarly, analyses performed using the EAS will also be performed using the ICCS-E.

8.2.1. Patient Description

8.2.1.1. Constitution of patients

Using the set of registered patients and set of patients with informed consent, the following patients will be aggregated: registered patients or patients with informed consent; observation-completed patients; patients included in the SAS; and patients included in the EAS. In addition, patients with no CRF collected, patients excluded from the SAS, and patients excluded from the EAS will be aggregated. Patients excluded from the SAS/EAS will be aggregated also by reason for exclusion.

8.2.1.2. Treatment discontinuations and dropouts

Using the SAS and EAS, patients who discontinued treatment will be summarized overall and by timing (within 24 hours, >24 hours; [as a further categorization for >24 hours] >24 to ≤72 hours, >72 hours) in terms of n and proportion. Patients who discontinued treatment will be summarized also by reason for discontinuation in terms of n and proportion.

8.2.1.3. Patients excluded from analysis

Patients excluded from the SAS and those excluded from the EAS will be listed in tabular form with their reason for exclusion.

8.2.2. Patient Characteristics and Medical History

8.2.2.1. Patient characteristics

Using the SAS and EAS, patients will be, according to the methods described in Section 8.1, summarized with respect to the following patient characteristics:

- Gender [male, female]
- Age (years) (continuous)
- Age 2 [newborn (≤27 days from birth), non-newborn (≥28 days from birth)]

- Age 3 [≥45 weeks of corrected gestational age to <12 months of age, ≥12 to <24 months of age, ≥2 to <6 years, ≥6 to <18 years]
- Body weight (continuous)
- Body Mass Index (BMI) (continuous)
- Hepatic function disorder [absent, present]
- Renal impairment [absent, present]
- Surgery [absent, present]
- Operative procedure [cardiovascular, neurosurgery, abdominal, other]
- Use of heart-lung machine [absent, present]
- American Society of Anesthesiologists (ASA) classification [Class 1, Class 2, Class 3, Class 4, Class 5, Class 6]
- Complications [absent, present]

Using the SAS, a breakdown of patients regarding the following factors will be presented in terms of n and proportion by SOC and preferred term (PT):

- Past history
- Complication
- Primary disease

Using the SAS and EAS, patients will be summarized by each of the following factors in terms of n and proportion:

- Concomitant use of another sedative or analgesic [absent, present]
- Another sedative or analgesic used concomitantly [midazolam, fentanyl, morphine, other]

8.2.2.2. Dosing status of Precedex

Using the SAS, dosing data of this drug will be summarized regarding the following aspects:

- Duration of treatment (hours) (continuous)
- Duration of treatment (hours) [≤24 hours, >24 hours; (as a further categorization for >24 hours) >24 to ≤72 hours, >72 hours]
- Infusion rate (μg/kg/h) (continuous)
- Reason for modification/termination [sedation management ended, diurnal variations maintained, oversedation, insufficient sedation, AEs, other]
- Dosage form of this drug [vial, prefilled syringe]
- Dilute concentration (for vial only) [4 μg/mL, other; (as a further categorization for "other") >4 μg/mL, <4 μg/mL]

The duration of treatment should be given by the period from the start of the first administration of this drug to the time administration of this drug was last confirmed including non-dosing periods.

The infusion rate will be summarized both overall and by Age 1 [≥45 weeks of corrected gestational age to <6 years of age, ≥6 to <18 years].

8.2.3. Safety Analyses

For safety endpoints, events that developed from the start of treatment to 24 hours after the end of treatment will be included in a summarization. For the purpose of listing, all events reported in this study will be used.

8.2.3.1. Adverse reactions

8.2.3.1.1. All adverse reactions

Adverse reactions will be summarized by SOC and PT in terms of n and proportion.

The duration of treatment with this drug to the first onset of an adverse reaction and accumulated dose to that time will be summarized by SOC and PT. In addition, patients who experienced adverse reactions will be summarized by SOC and PT in terms of n and proportion for different age categories (≥45 weeks of corrected gestational age to <12 months of age, ≥12 to <24 months of age, ≥2 to <6 years, and ≥6 to <18 years).

8.2.3.1.2. Serious adverse reactions

Serious adverse reactions will be summarized by SOC and PT in terms of n and proportion.

The duration of treatment with this drug to the first onset of a serious adverse reaction and accumulated dose to that time will be summarized by SOC and PT.

8.2.3.1.3. Details of adverse reactions

Adverse reactions in different categories defined with respect to the following factors will be summarized by SOC and PT in terms of n and proportion:

- Seriousness [serious, non-serious]
- Known/unknown [known, unknown]
- Action taken for this drug [discontinued, dose reduced, no change, dose increased, other]
- Outcome [not recovered, recovered with sequelae, improved, resolved/recovered, unknown]

For these summarizations, patients who experienced multiple adverse reactions of the same adverse reaction (identical PT) will be handled as follows:

- For seriousness: Patients who experienced both serious and non-serious adverse reactions of the same PT will be handled as having experienced a serious event.

- For known/unknown: Priority will be given to “unknown”.
- For time to onset: The days to the first onset will be used.
- For action taken: If multiple actions were taken, only one kind of action will be adopted with the order of priority being discontinued, dose reduced, no change, dose increased, and other.
- For outcome: The outcome for the last event will be used.

8.2.3.1.4. Safety specification

The following adverse reactions in the scope of the safety specification will be summarized in terms of n and proportion.

- *Important Identified Risks: bradycardia, hypotension, hypertension, hyperglycaemia, withdrawal syndrome, and respiratory depression*
- *Important Potential Risks: atrioventricular block, cardiac arrest, convulsions, cortisol suppression, hypothermia, ischaemic heart disease, and tachypnoeic potential*

8.2.3.1.5. Onset time of adverse reactions

Adverse reactions that developed before and after the end of treatment will be separately summarized by SOC and PT in terms of number of patients.

8.2.3.1.6. Adverse reactions in patients excluded from the safety analysis set

Adverse reactions occurring in CRF-collected patients who are excluded from the SAS will be listed in tabular form. In addition, those adverse reactions will be summarized by SOC and PT in terms of number of patients.

8.2.3.2. Adverse events

8.2.3.2.1. All adverse events

AEs will be summarized by SOC and PT in terms of n and proportion.

AEs that developed in patients in different age categories (≥45 weeks of corrected gestational age to <12 months of age, ≥12 to <24 months of age, ≥2 to <6 years, and ≥6 to <18 years) will be summarized by SOC and PT in terms of n and proportion.

8.2.3.2.2. Serious adverse events

SAEs will be summarized by SOC and PT in terms of n and proportion.

The duration of treatment with Precedex to the first onset of an SAE and accumulated dose to that time will be summarized by SOC and PT.

8.2.3.3. Other endpoints

Not applicable.

8.2.3.4. Subgroup analyses

Patients in each relevant subgroup defined in Section 5.4 who experienced at least one adverse reaction will be summarized in terms of n and proportion. In addition, risk ratios for the comparison of proportion between subgroups will be presented according to Section 8.1.3. If events developed in <10 patients within a subgroup, the risk ratio for the subgroup may not be determined if it is found to be difficult after reconsideration of the subgroup.

Similar subgroup analyses will be performed also for serious adverse reactions and SAEs.

For the subgroups with and without concomitant use of midazolam, fentanyl, morphine, and other drugs, patients who experienced at least one adverse reaction will be summarized in terms of n and proportion. Only patients in which an adverse reaction developed after the start of the use of the concomitant drug considered will be counted. According to Section 8.1.3, the risk ratio based on the proportion of patients will be determined for the subgroups; for those in which events developed in <10 patients, however, the risk ratio may not be determined if it is found to be difficult after reconsideration of the subgroup.

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8.2.4. Effectiveness Analyses

8.2.4.1. Overall effectiveness assessment

The effectiveness proportion ([%]: number of responders/[number of responders + number of non-responders]) will be calculated.

8.2.4.2. Subgroup analyses

Overall effectiveness assessment will be performed for different subgroups defined with respect to each of the relevant factors in Section 5.4.

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9. LISTINGS

The following patients and events will be listed in tabular form (the sets indicated in parentheses represent the patient sets used for the listing):

- Patients included in the study (CRF-collected patients, informed consent-completed patients)
- Patients who experienced AEs (SAS, informed consent-completed patients)

- Patients who experienced adverse reactions (SAS, informed consent-completed patients)
- Patients excluded from the SAS who experienced adverse reactions (CRF-collected patients)
- Patients who experienced serious adverse reactions (SAS)
- Patients who experienced SAEs (SAS)
- Patients with hepatic function disorder who experienced adverse reactions (SAS)
- Patients with renal impairment who experienced adverse reactions (SAS)
- Events included in the scope of the safety specification (SAS, informed consent-complected patients)
- Patients who experienced an event in the safety specification as an adverse reaction (SAS, informed consent-complected patients)

In addition, documents required for periodic safety reporting or application for re-examination will be prepared, as necessary.

10. APPENDICES

10.1. Appendix 1: Example of Tabulated Presentation of Risk Ratios for Different Subgroups Regarding the Proportion of Patients with an Adverse Reaction

Event name: Increased XXX	Category 1		Category 2		Risk ratio (RR)	
	n/N	(%)	n/N	(%)	RR	95% CI
Gender (male vs. female)	18/2220	(0.8)	3/1099	(0.3)	2.97	(0.88-10.06)
≥65 yrs vs. <65 yrs	19/2788	(0.7)	2/531	(0.4)	1.81	(0.42-7.74)
Diagnosis (disease A vs. disease B)	3/221	(1.4)	18/3098	(0.6)	2.34	(0.69-7.87)
Duration of disease (<1 yrs vs. ≥1 yrs)	9/771	(1.2)	7/866	(0.8)	1.44	(0.54-3.86)
Drug A - concomitant use (present vs. absent)	9/798	(1.1)	12/2521	(0.5)	2.37	(1.00-5.60)
Drug A - pretreatment (present vs. absent)	1/148	(0.7)	20/3171	(0.6)	1.07	(0.14-7.93)
Disease B - complication (present vs. absent)	16/1614	(1.0)	5/1703	(0.3)	3.38	(1.24-9.20)
Disease B - past history (present vs. absent)	7/674	(1.0)	14/2643	(0.5)	1.96	(0.79-4.84)
Hepatic function disorder (present vs. absent)	0/80		18/2056	(0.9)		
Renal impairment (present vs. absent)	1/140	(0.7)	17/2004	(0.8)	0.84	(0.11-6.28)

10.2. Appendix 2: Retrieval Conditions for Hepatic Function Disorder/Renal Impairment

The following MedDRA Standardised MedDRA Queries (SMQs) and High Level Group Terms (HLGTs) will be used to retrieve patients with hepatic function disorder/renal impairment:

	SMQ	HLGT
Hepatic function disorder, present	● Hepatic disorders (Narrow)	● Hepatic and hepatobiliary disorders ● Hepatobiliary neoplasms

Renal impairment, present	● Acute renal failure (Narrow) ● Chronic kidney disease (Narrow) ● Renovascular disorders (Narrow)	● Nephropathies ● Renal disorders (excl nephropathies)