(Appendix)

Precedex® Intravenous Solution Special Investigation (in pediatric patients)

FULL PROTOCOL

Pfizer Japan Inc.

STUDY INFORMATION

Title	Precedex® Intravenous Solution Special Investigation (in pediatric patients)
Protocol number	C0801023
Protocol version identifier	Version 5
Date	10 February 2022
Active substance	Dexmedetomidine Hydrochloride
Medicinal product	Precedex® Intravenous Solution 200 µg "PFIZER" Precedex® Intravenous Solution 200 µg/ 50 mL syringe "PFIZER"
Research question and objectives	To assess the data, including safety profile, of Precedex® Intravenous Solution administered for "sedation during and after mechanical ventilation in the intensive care setting" in pediatric patients under actual medical practice.
Author	PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
ASA	American Society of Anesthesiologists
CRF	Case Report Form
EDC	Electronic Data Capture
EDP	Exposure During Pregnancy
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MHLW	Ministry of Health, Labour and Welfare
NIS	Non-Interventional Study
PMDA	Pharmaceuticals and Medical Devices Agency
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set

3. RESPONSIBLE PARTIES

The Japan Good Post-marketing Study Practice officer

4. AMENDMENTS AND UPDATES

Protocol version identifier	Date	Revised sections	Summary of revisions	Reason
Version 5	10 February 2022	Information about this study 5 8.2.3 13 17.1	Change in study organization Prolongation of both investigation and registration periods Enlargement of the scope of work contracted Change in study organization	Because it has been determined that the investigation period is to be prolonged for 1 month and the registration period for 2 months, considering the possibility that the study cannot accrue the target number of patients in the SAS by the end of the planned study period. Also, because of a change in study organization and enlargement of the scope of work contracted.
Version 4	1 October 2021	5 8.2.3 17.2	Prolongation of both investigation and registration periods Change in the Contact information for inquiries about the EDC system Other editorial revisions	Because it has been determined that both investigation and registration periods are to be prolonged for 2 months, considering the possibility that the study cannot accrue the target number of patients in the SAS by the end of the planned study period.
Version 3	25 February 2021	5 8.2.3	Prolongation of both investigation	Because it has been determined that both investigation and registration periods are

Protocol version identifier	Date	Revised sections	Summary of revisions	Reason
			and registration periods	to be prolonged for 5 months, considering the possibility that the study cannot accrue the target number of patients in the SAS by the end of the planned study period.
Version 2	24 July 2019	10	Addition of the section	Because contents that had been described in another document were incorporated in this protocol.
Version 1	14 February 2019	NA	NA	NA

5. MILESTONES

Milestone	Planned date
Start of data collection	April 2019
End of data collection	May 2022
Final study report	Around 2022

6. RATIONALE AND BACKGROUND

Precedex® Intravenous Solution (nonproprietary name: dexmedetomidine hydrochloride) (hereinafter referred to as "this drug") is an active dextrorotatory form (D-form) of medetomidine with an imidazole skeleton and is a potent and highly selective central α_2-adrenoceptor agonist. In Japan, its marketing approval was granted for the indication of "sedation during mechanical ventilation and after extubation in patients managed in the intensive care setting and able to be extubated early" in January 2004, for the indication of "sedation during and after mechanical ventilation in the intensive care setting" in August 2010, and for the indication of "sedation during surgery and procedures without intubation under local anesthesia" in June 2013. Regarding "sedation during and after mechanical ventilation in the intensive care setting," an application for approval of partial changes in approved items for marketing was filed in December 2017 and an indication for pediatric dosage and administration was approved in November 2018.

Among adverse events (AEs) for which a causal relationship with this drug could not be ruled out that were observed in a phase 3 multicenter, single-arm, open-label study to investigate the efficacy, safety, and pharmacokinetics of this drug in pediatric intensive care (C0801017), bradycardia, hypotension, and respiratory depression were observed in 12.7% (8/63 patients), 7.9% (5/63 patients), and 3.2% (2/63 patients), respectively, as events related to the safety specification. All of these events have already been reported in patients treated with this drug, and no noteworthy AEs were observed in this study. For these reasons, it was considered that if this drug was used for the purpose of "sedation during and after mechanical ventilation in the intensive care setting" in pediatric patients, the risks of these events were unlikely to increase markedly. In addition, risks associated with this drug have been identified based on the overseas use experience, and therefore it is considered that there is no major concern about the use in Japan.

However, since inclusion/exclusion criteria and restricted concomitant medications were specified for study patients in the Japanese study C0801017, it was considered useful to accumulate data under actual medical practice in Japan and examine the safety of this drug. In the Japanese study C0801017, the patients undergoing elective surgery were only those undergoing cardiovascular surgery, and the number of patients in internal medicine was limited. For these reasons, it was considered significant to make efforts for collecting information from multiple clinical departments, including departments other than cardiovascular surgery and to assess the safety, etc. of this drug in pediatric patients under actual medical practice.

Based on the above, the special investigation of Precedex® Intravenous Solution (in pediatric patients) (hereinafter referred to as "this study") will be conducted 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.

This study shall be conducted in strict compliance with the "MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171, dated December 20, 2004), the "Enforcement of the MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (PFSB Notification No. 1220008, dated December 20, 2004), "MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-Marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices and to Partially Amend the MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 26, dated March 11, 2013), the "Enforcement of the MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-Marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices, and to Partially Amend the MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (PFSB Notification No. 0311-7, dated March 11, 2013), "MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 116, dated October 26, 2017), and "Announcement of the MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products (Regarding the

MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products)" (PSEHB Notification No. 1026-1, dated October 26, 2017).

7. RESEARCH QUESTION AND OBJECTIVES

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.

7.1. Safety specifications

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

7.2. Concerns for efficacy

Effectiveness by type of surgical procedure and type of clinical department in pediatric patients

8. RESEARCH METHODS

8.1. 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.

8.2. Setting

Patients who meet the registration criteria will be included in this study.

8.2.1. Registration criteria

Pediatric patients (45 weeks corrected gestational age to <18 years old) administered this drug for "sedation during and after mechanical ventilation in the intensive care setting"

Refer to the latest package insert of this drug for "INDICATIONS," "DOSAGE AND ADMINISTRATION," and "PRECAUTIONS" when this drug is administered.

8.2.2. Study sites

The study is scheduled to be conducted at approximately 20 sites including intensive care departments and anesthesiology departments, etc. for both Maruishi Pharmaceutical Co., Ltd. and Pfizer Japan Inc.

8.2.3. Planned study period

The planned period covered by this study is as follows.

Investigation period: April 2019 to May 2022 (from the start of registration to the completion of the observation period of the last patient)

Registration period: April 2019 to April 2022

The registration is terminated if the target number of the patients has been collected, even before the end of the registration period.

8.2.4. Study procedures

8.2.4.1. Study method

Continuous registration system: This study will be conducted with continuous registration system that patients who meet the conditions of this study will be registered sequentially until data are collected on a target number of patients.

8.2.5. Observation period

From the start of administration of this drug to the discharge from the intensive care unit (ICU). However, if the patient leaves the ICU before 24 hours after the end of administration of this drug, AEs observed up to 24 hours after the end of administration should be entered in the CRF as much as possible, and the AEs should be monitored until the outcomes become known as far as possible.

8.3. Variables

This study will be conducted according to the following schedule of observation.

Table 1. Variables and schedule of observation

Variable	Registration form	CRF At the start of administration of this drug	CRF From the start of administration of this drug to ICU discharge	CRF Until 24 hours after the end of administration of this drug
ID number	●	*		
Sex	●	*		
Birth year and month	●	*		
Corrected gestational age [a]	●	*		
Date of start of administration of this drug	●			
Neonatal status [b]		●		
Height		●		
Body weight		●		
Pregnancy status [c]		●		
Primary disease		●		
Medical history		●		
Complication		●		
Surgery status		●		
Surgery name [d]		●		
Presence or absence of heart-lung machine [d]		●		
ASA classification [d]		●		
Date/time of entering the operating room [d]		●		
Date/time of leaving the operating room [d]		●		
Start date/time of surgery [d]		●		
End date/time of surgery [d]		●		
Date/time of ICU admission			●	
Date/time of ICU discharge			●	
Start date/time of mechanical ventilation			●	
Method of mechanical ventilation			●	
End date/time of mechanical ventilation			●	
Targeted drug use record			●	
Concomitant therapy (Drug therapy)			●	
Effectiveness [e]			●	
Adverse events [f]			●	●

* Some elements in the Registration Form are automatically reflected in the CRF. The investigators should check and update the CRF as needed.
a. Enter the information only if the age at the start of administration of this drug is less than 1 year old.
b. Enter the information only if the age at the start of administration of this drug is 0 months of age.
c. Enter the information only if the sex is "Female."
d. Enter the information only if the surgery status is "Yes."
e. At the end of administration of this drug, overall effectiveness evaluation of this drug will be performed, and the results will be entered.
f. If the patient leaves ICU before 24 hours after the end of administration of this drug, AEs observed up to 24 hours after the end of administration should be entered in the CRF as much as possible, and the AEs should be monitored until the outcomes become known as far as possible.
ASA: American Society of Anesthesiologists, ICU: intensive care unit

8.3.1. Patient characteristics

1. The information at the start of administration of this drug will be recorded in registration form.

   a. ID number

b. Sex

c. Birth year and month

d. Corrected gestational age (only if <1 year old)

e. Date of start of administration of this drug

2. The following information will be recorded in CRF.

<Basic Patient Information (at the start of administration of this drug)>

a. ID number

b. Sex

c. Birth year and month

d. Corrected gestational age (only if <1 year old)

e. Neonatal status (only if 0 months of age)

f. Height

g. Body weight

h. Pregnancy status (only if the sex is “Female”)

i. Primary disease

j. Medical history

k. Complication

<Surgery Information>

l. Surgery status

(Enter information from “m. Surgery name” to “s. End date/time of surgery” only if the surgery status is “Yes”)

m. Surgery name

n. Presence or absence of heart-lung machine

o. American Society of Anesthesiologists (ASA) classification

p. Date/time of entering the operating room

q. Date/time of leaving the operating room

r. Start date/time of surgery

s. End date/time of surgery

< ICU Information>

t. Date/time of ICU admission

u. Date/time of ICU discharge

v. Start date/time of mechanical ventilation

w. Method of mechanical ventilation

x. End date/time of mechanical ventilation

8.3.2. Administration record of targeted drug

Regarding the use status of this drug during the observation period, the following information will be recorded:

1. Name of the clinical department of the physician administering this drug
2. Dosage form
3. Dilute concentration
4. Start date/time of administration; Infusion rate
5. Date/time of infusion rate change; Infusion rate; Reason
6. End date/time of administration; Reason

8.3.3. Concomitant therapy

8.3.3.1. Drug therapy

Regarding drugs used for sedation, analgesia, and anesthesia for surgery during the period of administration of this drug, the following information will be recorded:

1. Drug name (product name)
2. Dose or infusion rate
3. Start date/time of administration
4. End date/time of administration

8.3.4. Investigation completion (discontinuation) record (including the reason for discontinuation)

The end date/time of the observation period or the date/time of discontinuation will be entered, and only one of the following will be selected and entered as completion or the primary reason for discontinuation. If AE or death is selected, the information will also be entered in the AE section.

1. Completion
2. AE
3. Death
4. Lost to follow-up
5. Others

8.3.5. Effectiveness evaluation

At the end of administration of this drug, overall effectiveness evaluation of this drug will be performed, and the results will be recorded.

1. Effectiveness evaluation
    - Effective
    - Not effective
    - Indeterminate (In this case, the reason should be recorded.)

8.3.6. Adverse events

Occurrence of AEs from the start date of administration of this drug to the end date of observation period should be confirmed and the following information should be recorded. Also, further investigation should be separately conducted, if deemed necessary by Sponsor for patients who experienced a serious adverse reaction, an unexpected adverse reaction or other adverse reactions not listed in the package insert.

- Presence/absence of AE
- Name of AE
- Date of occurrence
- Intervention
- Seriousness

- Outcome up to the present
- Causal relationship to this drug

8.4. Data sources

In this study, the investigators transcribe the necessary information from the medical record under daily medical practice in accordance with the protocol.

8.5. Study size

8.5.1. Planned sample size

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

8.5.2. Rationale for sample size

When 100 patients are collected, AEs with a true incidence of 3% or higher would be observed in 1 or more subjects with a probability of 95% or higher. Based on the incidence proportions of bradycardia, hypotension, and respiratory depression observed in the Japanese study C0801017 for which a causal relationship with this drug could not be ruled out (12.7%, 7.9% and 3.2%, respectively), these events were considered to be observable. Events related to the safety specification but with unknown incidence in Japanese pediatric patients would be collected as much as possible in this study. For rare events, routine pharmacovigilance activities such as spontaneous reports would also be utilized for evaluation.

8.6. Data management

8.6.1. CRFs/Electronic data record

A CRF in this protocol refers to the record of electronic data corresponding to the method of data collection during this study.

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

The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

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.

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

8.6.2. Record retention

The records related to this study should be retained at the study site until the End of Study Letter by Pfizer is received or during the period defined by the study site, whichever is longer.

8.6.3. Data collection method

The data for this study will be entered and confirmed by using the electronic system on the internet designed for collecting post-marketing survey data (Electronic Data Capture, EDC, hereinafter referred to as “this system”).

8.6.4. Patient registration

The investigator will enter information on the patient registration screen of this system (the registration form) and save the data. Patient registration will be performed immediately after the first administration with this drug.

If information in the registration form require confirmation, the investigator may be requested to perform follow-up survey and respond to the query. Registration will be fixed after the query is resolved.

8.6.5. Points to consider for completion, revision, and submission of CRF

8.6.5.1. Data entry

The investigator should confirm the survey items and enter the data into this system based on information in the medical charts.

8.6.5.2. Data revision

Upon receiving query from Sponsor on the contents of the CRF (follow-up survey), the investigator will again confirm the information in the medical charts, and as required, correct relevant sections and save the data.

8.6.5.3. Submission

After data entry and revision are completed, CRFs should be signed electrically by the investigator following confirmation of entry and follow-up survey.

8.7. Data analysis

1. Definition of analysis set

The SAS consists of a full analysis set (FAS) that is as closer as possible to all patients who received this drug. The effectiveness analysis set consists of patients included in the SAS considered evaluable for effectiveness according to the separately prescribed Statistical Analysis Plan (SAP) of this study.

2. Analysis method

   - Analysis for safety evaluation

   Events for which a causal relationship with this drug could not be ruled out are considered as adverse drug reactions (ADRs). The number of patients with ADRs and the proportion ([%]: number of patients with ADRs/number of patients included in the SAS) will be calculated.

   - Analysis for effectiveness evaluation

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

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.8. Quality control

Prior to conducting the study, the site staff will explain to the investigator about the contents of the protocol, etc. and ask the investigator for completion of a CRF based on medical charts.

8.9. Limitations of the research methods

There may be potential limitations in this study:

1. Since no control group is included in this study, there is a limitation in determining whether or not a risk of developing AEs and adverse reactions increases with administration of the study drug.

2. Due consideration may not be given to confounding factors due to insufficient background information collected.

3. Since this study collects the information described in medical charts, specified data may not be collected or may be missing.

8.10. Other aspects

Not applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

9.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, or it is an information provision based on the law (even though that involve data subject to privacy laws according to applicable legal requirements), obtaining informed consent from patients by Pfizer is not required with regard to the personal information provision from the study site to Pfizer. Also, because the report of information or results collected in this study to the local regulatory authority or healthcare providers by Pfizer as needed is an information provision based on the law, obtaining informed consent from patients by Pfizer is not required.

In this study, Pfizer will collect information that cannot identify specific patients from the study sites. The results of this study, which are prepared not to identify specific patients, may be reported to Pfizer Inc., which is the corporate parent of the sponsor of this study, or Group companies, or regulatory authorities in other countries, as needed, or published it as a presentation at academic conferences or manuscript for the purpose of providing proper use information for this drug. If these information falls under personal information of the Personal Information Protection Act, these actions may not be based on the laws or regulations, and therefore, may correspond to provision to the third party and using the information for purposes other than business that require consent from the patient. Therefore, the study sites will obtain written or verbal consent from the patients to be included in this study so that Pfizer can use the results of this study to report to Pfizer Inc., group companies or regulatory authorities in other

countries, or to present it at academic conferences or publish manuscript, etc. Whether consent is obtained from patients or not is described in the CRF. The original of the written informed consent form should be retained by the study investigator.

In general, the investigator must obtain consent from a patient personally. However, if the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted or he or she is a minor, consent is obtained from legally acceptable representative or parent(s). In this case, every effort should be made to obtain the patient's assent as far as possible after obtaining consent from legally acceptable representative or parent(s) if the patient is a minor. If the study patient does not provide his or her own consent, the source documents must record the relationship of the person signing the consent and the patient (e.g., parent(s), spouse). If a minor registered in the study reaches adulthood during the study, the consent will be reacquired as far as possible from the patient at the time of adulthood according to Japanese law.

At the time of obtaining informed consent, the investigator must use informed consent form and other materials and ensure that each study patient, or his or her legally acceptable representative, or parent(s) if a minor, is fully informed about the information provided to Pfizer and the objectives of use and possible risks associated with consent.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

In this study, review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) is not required.

9.4. Ethical conduct of the study

This study will be conducted in compliance with the “MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products” (MHLW Ordinance No. 171, dated December 20, 2004). Also, the study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events to Pfizer Safety Unit using the Non-Interventional Study Adverse Event Report Form (NIS AE Report Form). These requirements are specified for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events."

Safety event	Recorded on the case report form	Reported on the NIS AE Report Form to Pfizer Safety Unit within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) Note: Any associated AE is reported together with the exposure scenario.

For each AE, 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 a SAE (refer to the section "Serious adverse events" below).

Safety events listed in the table above must be reported to Pfizer Safety Unit within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to this drug**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the date and time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the 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. Any information relevant to the event, such as concomitant medications and complications, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

10.2. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of this drug, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety Unit (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and he or she considers the SAE to be related to this drug, the SAE also must be reported to Pfizer Safety Unit.

10.3. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to this drug, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that this drug caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and he or she cannot determine whether this drug caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but he or she determines that this drug did not cause the event, this should be clearly documented on the CRF and the NIS AE Report Form.

10.4. Definitions of safety events

10.4.1. Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. The same definition is applied for medical devices and nutritional products (including infant and toddler formulas [hereinafter "pediatric formulas"]). Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependence.

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;

- Occupational exposure.

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 drug dosing or discontinuation from the study, 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 result, 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.

10.4.2. Serious adverse events

An SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose or using a medical device that:

- Results in death;
- Is life-threatening;
- Requires hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/dysfunction (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 patient or may require intervention to prevent one of the other outcomes listed in the definition above, 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 dependence or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. Such event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected infectious transmission" and "infection transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by the Safety Unit. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

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

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a sudden change in clinical conditions (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for laboratory tests and/or procedures required by the study protocol)

10.4.3. Scenarios necessitating reporting to Pfizer Safety Unit within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) this drug, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to this drug (maternal exposure).

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

2. A male has been exposed, either due to treatment or environmental exposure to this drug prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence/absense of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with this drug, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AE Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to this drug in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AE Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the expected delivery date (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate should 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 aborted 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 (e.g., extrauterine pregnancy, spontaneous abortion, intrauterine fetal death, neonatal death, or congenital anomaly [in a live born, an aborted fetus, an intrauterine fetal death, or a neonatal death]), the procedures for reporting SAEs should be followed.

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 this drug.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence/absence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accordance with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error, which could have been prevented from occurring, and may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to drug name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence/absence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
    - An identifiable reporter;
    - A suspect product;
    - The event medication error.

Overdose, misuse, and extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reportable to Pfizer by the investigator, irrespective of the presence/absence of an associated AE/SAE.

Lack of efficacy

Reports of lack of efficacy to a Pfizer product are reportable to Pfizer by the investigator, irrespective of the presence/absence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational exposure

Reports of occupational exposure to a Pfizer product are reportable to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.5. MEDICAL DEVICE COMPLAINT REPORTING REQUIREMENTS

All complaints about medical devices, regardless of whether the medical device complaint is associated with an AE, will be collected on the applicable pages within the CRF. This includes potential incident or malfunctions associated with the use of a medical device product. An incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again, might have led to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of awareness of the event by the investigator.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Information collected in this study will be used for reporting purposes to report Ministry of Health, Labour and Welfare (MHLW), Pharmaceuticals and Medical Devices Agency (PMDA), Pfizer Inc., which is the corporate parent of the sponsor of this study, and the group companies, or regulatory agency in other countries. Also, it will be used for submitting application of re-examination (including Periodic Safety Update Report), re-evaluation, preparation of material for proper use information of this drug, publications and activities for information provision. In addition, Pfizer may disclose the study results to provide information for proper use, as needed, on www.clinicaltrials.gov (ClinicalTrials.gov), as presentations at academic conferences, or as manuscripts, etc.

Data obtained from the patients registered in this study will be reported to the MHLW pursuant to the Pharmaceutical and Medical Device Act. In this case, the data may be publicly posted in MHLW's “Pharmaceutical and Medical Device Safety Information” and “Pharmaceuticals and Medical Devices Information Website (https://www.pmda.go.jp) ” as a listing of patients, which will include the names of drugs, adverse reactions, sex, age (increment of 10 years), and other relevant information. Furthermore, data collected may also be disclosed if the MHLW is required to disclose such information in accordance with the “Act on Access to Information Held by Administrative Organs” (Law No. 42 dated May 14, 1999); provided that in no event will the names of physicians, medical institutions, and other personal information be subject to such disclosure, nor will it be posted or disclosed.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

12. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION

Refer to the appendix 1 of the risk management plan “Organizational structure for safety management and post-marketing surveillance, etc.”

13. NAME, AND ADDRESS OF CONTRACTOR AS WELL AS SCOPE OF WORK CONTRACTED

Company name: PPD
Address: PPD
Scope of work contracted: Works related to planning of study, drafting of plan, operating the study, monitoring, etc.

Company name: PPD
Address: PPD
Scope of work contracted: Establishment, operation and maintenance of the EDC system, and research service other than management of the Post-Marketing Study, etc.

Company name: PPD
Address: PPD
Scope of work contracted: Registration, establishment of the EDC system, data management, statistical analysis, and research service other than management of the Post-Marketing Study, etc.

14. ADDITIONAL MEASURES THAT MAY BE IMPLEMENTED BASED ON THE STUDY RESULTS AND CRITERIA FOR DETERMINATION OF THE INITIATION

Review the risk management plan including the following contents at the scheduled timing of milestones.

1. Review the necessity for changing the contents of risk minimization activities for the current safety specifications.
2. Review the necessity for changing the contents of this study plan including the presence or absence of new safety specifications (continuation of the study, implementation of additional study, etc.).
3. Review the necessity for formulating risk minimization measures for new safety specifications.

15. SCHEDULED TIMING OF MILESTONES AND THEIR RATIONALES FOR EVALUATION OF STUDY IMPLEMENTATION STATUS AND RESULTS AND REPORTING TO THE PMDA

At the time of making periodic safety reports and at the end of the survey. To comprehensively examine safety information. The interim analysis results will be reported at the time of making the first periodic safety report after the CRFs for 50 subjects have been fixed.

16. OTHER NECESSARY MATTERS

Not applicable

17. CONTACT INFORMATION

17.1. Contact information for inquiries about the study

Name	PPD
Address	PPD
FAX	PPD
E-mail address	PPD

17.2. Contact information for inquiries about the EDC system

Name	PPD
Business Hours	
TEL	PPD
E-mail address	

18. REFERENCES

Not applicable

19. LIST OF TABLES

20. LIST OF FIGURES

Not applicable

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable

ANNEX 2. ADDITIONAL INFORMATION

A. Special Investigation registration form

B. Special Investigation case report form