PAXLOVID® PACK General Investigation

FULL PROTOCOL

Pfizer Japan Inc.

STUDY INFORMATION

Title	PAXLOVID® PACK General Investigation
Protocol number	C4671018
Protocol version identifier	Version 3
Date	31 January 2023
Active substance	Nirmatrelvir/ritonavir
Medicinal product	PAXLOVID® PACK
Research question and objectives	To assess the safety and effectiveness of PAXLOVID under actual status of use.
Author	PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
3CL	3C-like protein
COVID-19	Coronavirus disease 2019
EDC	Electronic data capture
FDA	Food and drug administration (United States)
ICH	International conference on harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
N/A	Not applicable
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

3. RESPONSIBLE PARTIES

The Japan Good Post-marketing Study Practice officer

4. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
Amended 2	31 January 2023	5. MILESTONES	Addition of items and update of contents	Administrative changes
		6. RATIONALE AND BACKGROUND	Update of ministerial ordinances, notifications, etc.	Due to the partial revision of the ministerial ordinance
		8.9. Limitations of the research methods 9.4. Ethical conduct of the study	Terminology changes, etc.	Administrative changes
		10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS	Changes in Japanese translation, etc., and maintenance of descriptions	Due to changes in association with a revision of the in-house form
		12. NAME, AND ADDRESS OF CONTRACTOR AS WELL AS SCOPE OF WORK CONTRACTED	Maintaining address information	Administrative changes
		16.2. Contact information for inquiries about the EDC system (In the case of study using EDC)	Changes in contact information for inquiries	Due to changes in the information concerning contact information
Amended 1	28 June 2022	7.1. Safety specifications	Added anaphylaxis to important identified risks	Due to the revision of safety specification in the Risk Management Plan
		8.7. Data analysis	1. Definition of analysis set Change before:	The effectiveness analysis set was not a subset of safety populations,

			·Effectiveness Analysis Set 1: A population of patients in the SAS excluding patients for whom effectiveness evaluation is not reported at all or whose disease is not subject to the study After change: ·Effectiveness Analysis Set 1: A population of patients in which effectiveness can be evaluated among patients in which this drug was administered	but effectiveness evaluable among all patients with administration
		10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS	Changes in Japanese translation, etc., and maintenance of descriptions	Due to changes in association with a revision of the in-house form
		12. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION	Item Removal (Subsequent section numbers moved up)	Administrative changes associated with the Notification "Formulation and Publication of Risk Management Plans" dated 18 March 2022
FINAL	08 February 2022	N/A	N/A	N/A

5. MILESTONES

Milestone	Planned date
Start of investigation period	February 2022
Start of data collection (registration date of the first subject)	31 March 2022
End of investigation period	April 2024
End of data collection (release date of the database)	November 2024
Interim report	28 September 2022
Final study report	October 2025

6. RATIONALE AND BACKGROUND

PAXLOVID® PACK (generic name: nirmatrelvir tablets and ritonavir tablets) (hereinafter, this drug) is a combination of nirmatrelvir, an inhibitor of SARS-CoV-2 3CL protease, and ritonavir, a potent inhibitor of CYP3A4. The combination of the 2 drugs will maintain exposure to nirmatrelvir to inhibit viral replication throughout the treatment period. The marketing authorization of this drug was obtained in February 2022 in Japan for the indication of "Disease caused by SARS-CoV-2 infection (COVID-19)."

The objective of the "PAXLOVID® PACK General Investigation" (hereinafter, this study) is to assess the safety and effectiveness of this drug under post-marketing actual status of use.

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 on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, Medical Devices and Regenerative Medical Products" (MHLW Ordinance No. 135, dated September 22, 2004), the "Enforcement of the MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices, Regenerative Medical Products" (PFSB Notification No. 0812-4, dated August 12, 2014), "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

The objective of this study is to assess the safety and effectiveness of this drug under post-marketing actual status of use in patients receiving this drug.

7.1. Safety specifications

Important Identified Risks: Toxic epidermal necrolysis/oculomucocutaneous syndrome, hepatic function disorder and anaphylaxis

Important Potential Risks: Hyperglycemia/diabetes mellitus and bleeding tendencies

8. RESEARCH METHODS

8.1. Study design

This study is an open-label, multi-center, one arm prospective observational cohort study of patients receiving this drug. The investigators complete the CRF based on the information extracted from the medical record created in daily medical practice.

8.2. Setting

Patients who satisfy all of the registration criteria are subject to this study.

8.2.1. Registration criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in this study:

Patients who receive this drug for the first time.

In principle, data will be collected prospectively. However, in order to collect data at an early stage after approval as much as possible, patients who started to receive this drug before conclusion of the contract may be enrolled in this study.

Refer to the latest package insert of this drug for “indications” and “dosage and administration” when this drug is administered.

[Indications]
Disease caused by SARS-CoV-2 infection (COVID-19)
[Dosage and administration]
The usual dosage in adults and pediatric patients (≥12 years of age weighting ≥40 kg) is 300 mg of nirmatrelvir and 100 mg of ritonavir all taken together orally twice daily for 5 days.

8.2.2. Exclusion criteria

There are no exclusion criteria for this study.

8.2.3. Study sites

Plan to conduct this study at 400 sites including the Department of Infectious Diseases, Department of Internal Medicine, etc.

8.2.3.1. Site requirements

Sites where patients can be followed up at the time of the site visit or by telephone, home visit, etc. after administration of this drug.

8.2.4. Planned study period

The planned period covered by this study is as follows.

Investigation period: February 2022 to April 2024 (from the start of the registration period to the completion of the observation period of the last patient.)

Registration period: February 2022 to February 2024

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

8.2.5. Study procedures

8.2.5.1. Study method

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

8.2.5.2. Request for cooperation in the study and contract

1. The site staff will explain the outline of this study to the physicians who are registered at PAXLOVID® PACK Registration Center and plan to use this drug.

2. If the site is selected as a study site, the site staff will conclude a contract for this study with the site.

8.2.6. Observation period

From the start date of administration to 28 days after the completion of administration (The day after the completion of administration is Day 1.)

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 Until 28 days after the completion of administration of this drug
ID number	●	*
Gender	●	*
Birth year and month/age	●	*
Eligibility	●	
Start date of treatment with this drug	●	*
Height/body weight		●
History of smoking		●
Presence/absence of symptoms of the target disease, severity, and date of onset		●
Presence/absence of liver functional impairment and renal functional impairment, severity		●
Disease history		●
Prior medications for infections caused by SARS-CoV-2		●
History of SARS-CoV-2 vaccination		●
Presence/absence of pregnancy (only for women)		●
Presence/absence of findings of pneumonia attributable to infections caused by SARS-CoV-2 at the start of administration		●
Hospitalization status		●
Targeted drug use record		●
Concomitant therapy (Drug therapy/ Non-drug therapy)		●
Tests (virus/vital signs)		●
End-of-study/Discontinuation record (reason)		●
Effectiveness evaluation		●
Adverse events		●
Informed consent for publication of results		●

* Some elements in the Registration Form are automatically reflected in the CRF. The investigators should check and update the CRF as needed.

8.3.1. Patient characteristics

1. Enter the information at the start of administration of this drug into the registration form

- ID number
- Gender

- Birth year and month/age (if birth year and month cannot be disclosed, age at the start of administration of this drug)
- Start date of treatment with this drug
- Eligibility

2. The following will be recorded in CRF at the start of administration of this drug:

(ID number, gender, and birth year and month/age in the Registration Form are automatically reflected in the CRF. The investigators should check and update the CRF as needed.

- ID number
- Gender
- Birth year and month/age
- Height (cm)
- Weight (kg)
- History of smoking
- Presence/absence of symptoms of the target disease (disease for which this drug is used), severity, and date of onset

  The presence/absence of symptoms will be judged based on the clinical symptoms related to infections caused by SARS-CoV-2, including but not limited to the symptoms shown below.

  > Cough, shortness of breath or dyspnea, feeling hot, chills or shivering, fatigue (decreased energy or feeling tired), muscle pain or body pain, diarrhea (loose or watery stools), nausea (queasy), vomiting, headache, sore throat, stuffy or runny nose, dysosmia, dysgeusia, and findings of pneumonia

  Severity should follow the severity classification in the “Clinical Practice Guidance for New Coronavirus Infection COVID-19” (see Table 2).

Table 2. Severity classification

Severity	Oxygen saturation	Clinical status
Mild	$SpO_2 \geq 96\%$	No respiratory symptoms, or cough alone with no dyspnea No finding of pneumonia in either case
Moderate I No respiratory failure	$93\% < SpO_2 < 96\%$	Dyspnea, pneumonia findings
Moderate II Respiratory failure present	$SpO_2 \leq 93\%$	Oxygen required
Severe		Admitted to ICU or requiring mechanical ventilation

Note
• It is desirable to measure SpO_2 and objectively judge the state of oxygenation.
• In order to confirm the presence/absence of pneumonia, it is desirable to take measures against nosocomial infection and take chest CT scans to the extent possible.
• If there is a difference in severity between oxygen saturation and the clinical status, the higher severity should be assigned.
Excerpted from the Clinical Practice Guidance for New Coronavirus Infection COVID-19 Version 6.2 (27 January 2022)

- Presence/absence of liver impairment/renal impairment*, severity

*Liver impairment/renal impairment are not transient laboratory abnormalities but represent events that require clinical consideration and follow-up.

Reference

[Severity of hepatic impairment: Child-Pugh classification]

	1 point	2 points	3 points
Hepatic encephalopathy	None	Mild (I/II)	Coma (III or higher)
Ascites	None	Mild	Moderate or higher
Serum albumin level	>3.5 g/dL	2.8 to 3.5 g/dL	<2.8 g/dL
Prothrombin time	>70%	40% to 70%	<40%
Serum total bilirubin	<2.0 mg/dL	2.0 to 3.0 mg/dL	>3.0 mg/dL

A (mild), 5 to 6 points; B (moderate), 7 to 9 points; C (severe), 10 to 15 points

[Severity of renal impairment]

Severe: eGFR [mL/min/1.73 m^2] < 30
Moderate: 30 ≤ eGFR [mL/min/1.73 m^2] < 60
Mild: 60 ≤ eGFR [mL/min/1.73 m^2] < 90

- Clinical history (past history and concurrent illness)

  Enter complications that are risk factors for increasing severity.

- Prior medications for infections caused by SARS-CoV-2 (within 1 month prior to the start of administration of this drug)

  - Drug name
  - Period of administration
  - Reason for discontinuation

- History of SARS-CoV-2 vaccination (date of vaccination and name of vaccine)

8.3.2. Presence/absence of pregnancy (only for women)

The presence/absence of pregnancy from the start date of administration to the end of the observation period should be recorded.

8.3.3. Presence/absence of findings of pneumonia attributable to infections caused by SARS-CoV-2 at the start of administration

The presence/absence of findings of pneumonia attributable to infections caused by SARS-CoV-2 before the start of administration (including the start date of administration) should be recorded.

1. Date of evaluation
2. Presence/absence of findings of pneumonia

8.3.4. Hospitalization status

Regarding the status of hospitalization during the observation period, the following information should be recorded.

1. Presence/absence of hospitalization during the observation period
2. Date of admission (reason for admission)/date of discharge

8.3.5. Targeted drug use record

Regarding the status of use of this drug during the observation period, the following information should be recorded.

1. Dose per administration
2. Number of doses per day
3. Period of administration
4. Reason for change/interruption
5. Reason for discontinuation of administration (adverse events, other)

8.3.6. Concomitant therapy

8.3.6.1. Drug therapy

For all drugs used during the observation period, the following information should be recorded. If an adverse event is noted, the drugs used during the period from the start date of administration to the onset of the adverse event and medications used for treatment of the adverse event should also be recorded.

1. Drug name (product name)
2. Route of administration
3. Period of administration
4. Reasons for administration (infections caused by SARS-CoV-2, complications, adverse events, other)

8.3.6.2. Non-drug therapy

Regarding non-drug therapy for infections caused by SARS-CoV-2 performed during the observation period, the following information should be recorded. If an adverse event is observed, non-drug therapy used for the treatment of the adverse event should also be recorded.

1. The name of the therapy (oxygen administration, etc.)
2. Period of the therapy
3. Reason for the therapy (infections caused by SARS-CoV-2, adverse events, other)

8.3.7. Tests/clinical laboratory tests

8.3.7.1. SARS-CoV-2 viral test

Results of tests performed before administration (including the start date of administration) and during observation period should be recorded.

1. Date of tests
2. Sampling site
3. Test method (PCR/antigen test)
4. Results (viral load, etc.)
5. Type of variant of virus (wild type, Beta variant, Gamma variant, Delta variant, Omicron variant, etc.)

8.3.7.2. Vital signs

Results of tests performed before administration (including the start date of administration) and during observation period should be recorded.

1. Date of tests
2. Items of tests
    - Body temperature and percutaneous arterial oxygen saturation (SpO_2)

8.3.8. End-of-study / Discontinuation record

The end date of the observation period (date of medical examination on or after Day 28 after the completion of administration) should be recorded. If the patient cannot be followed up until Day 28 after the completion of administration (including Day 28), record date of discontinuation and select only one of the following items that corresponds to the primary reason. If the primary reason corresponds to patient death, necessary information should be recorded in the adverse event field.

1. End date of the observation period (date of examination on or after Day 28 after the completion of administration or date of discontinuation)
2. Status at the end
    - Completed
    - Symptoms improved
    - Death

- Transferred to other hospital
- Lost to follow-up
- Other

However, if the patient does not return for follow-up visit after the start of administration (including confirmation by telephone, etc.), the information should be recorded in the "lost to follow-up."

8.3.9. Effectiveness evaluation (severity)

The presence/absence of worsening of the severity of infections caused by SARS-CoV-2 after administration of this drug during the observation period (until Day 28 after the completion of administration [including Day 28]), highest severity, and presence/absence and severity of symptoms on the end date of the observation period (date of medical examination on or after Day 28 after the completion of administration) should be entered. For cases discontinuing observation in less than 28 days after the completion of administration, the highest severity by that point and the severity as of the date of discontinuation of the observation period should be recorded (see Table 2 for severity).

1. Worsening of severity after administration
   - Presence/absence of worsening of symptoms
   - Date of highest severity
   - Highest severity
2. Severity on the end date of the observation period
   - Date of evaluation
   - Presence/absence of symptoms of infections caused by SARS-CoV-2
   - Severity

8.3.10. Adverse events

Occurrence of adverse events from the start date of administration of this drug to the end date of the 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 adverse event
- Name of adverse event
- Date of occurrence
- Intervention
- Seriousness
- Outcome
- Causal relationship to this drug

If the adverse event is associated with abnormal laboratory values, i.e., clinical laboratory tests, the following information should also be recorded.

- Date of tests
- Name of laboratory test
- Site reference value
- Site unit
- Test results

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 full protocol.

8.5. Study size

8.5.1. Planned sample size

Target sample size: 3000 subjects (for safety analysis set)

8.5.2. Rationale for sample size

The incidence of adverse reactions to this drug in the phase 2/3 study (Study 4671005) was 7.8%. Assuming that the incidence of adverse reactions under the actual status of use in Japan is the same, adverse reactions will be detected in at least 214 patients with a probability of 90% with a sample size of 3000 patients. In order to detect, with a probability of 95%, at least 1 patient with an unknown adverse reaction occurring at a frequency of 0.1% or more, 3000 patients are required.

8.6. Data management

8.6.1. Case report forms (CRFs)/ Electronic data record

As used in this full protocol, the term CRF should be understood to refer to an electronic data record, depending on the data collection method used in 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 (or stamped “correction seal”), 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 (EDC)

The data for this study will be collected and confirmed by using the electronic system on the internet designed for collecting post-marketing survey data (Electronic Data Capture, EDC).

8.6.4. Patient registration (EDC)

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

If information in the registration form requires 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.

In this study, patients after the start of supply of this drug will also be registered regardless of the date of contract conclusion.

8.6.5. Points to consider for completion, revision, and submission of case report form (EDC)

8.6.5.1. Data entry

The investigator should confirm the survey items and enter the data into EDC based on medical records.

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 contents of medical records, 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 safety analysis set (SAS) consists of a full analysis set (FAS) that is as closer as possible to all patients who received this drug. Three effectiveness analysis sets are defined as follows.

   - Effectiveness Analysis Set 1: A population of patients in which effectiveness can be evaluated among patients in which this drug was administered
   - Effectiveness Analysis Set 2: A population of patients in Effectiveness Analysis Set 1 who are outpatients at the start of administration of this drug
   - Effectiveness Analysis Set 3: A population of patients in Effectiveness Analysis Set 2 who have risk factors for increased severity at the start of administration of this drug

2. Method of analysis

   - Analysis for safety evaluation

   Events possibly related to this drug are considered as adverse reactions. The number of patients with adverse reactions and the proportion [(%): number of patients with adverse reactions / number of patients included in the safety analysis set] will be calculated.

- Analysis for effectiveness evaluation

For Effectiveness Analysis Sets 1, 2, and 3, the number of patients by highest severity after administration of this drug and the number of patients by severity on the end date of the observation period will be tabulated.

For Effectiveness Analysis Set 1, the number of patients who died for any reason during the period from the start date of administration to Day 28 will be tabulated.

For Effectiveness Analysis Sets 2 and 3, the number of patients who have been hospitalized for treatment of infections caused by SARS-CoV-2 or died for any cause during the period from the start date of administration to Day 28 will be tabulated. The number of respective patients will also be tabulated. The number of these patients will also be tabulated in the subgroup of patients with no history of treatment with drugs for infections caused by SARS-CoV-2.

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in the SAP, which will be dated and retained by Pfizer. The SAP may modify the plans outlined in the full protocol; however, any significant modifications of definitions or analyses of endpoints will also 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 case report form based on medical records.

8.9. Limitations of the research methods

There may be potential limitations in this study:

1. Since no control group is included in the study, there is a limitation in determining whether or not a risk of developing adverse events and adverse reactions increases with administration of this 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 records, specified data may not be collected or may be missing.

8.10. Other necessary matters

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 institutions. 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 institutions 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 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 Ordinances in the section 6. RATIONALE AND BACKGROUND. 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 for recording and reporting

The table below summarizes the requirements for recording safety events on the CRFs and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated 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 CRF	Reported on the NIS AEM Report Form to Pfizer Safety 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 section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer 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 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 illnesses, 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 (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 s/he considers the SAE to be related to this drug, the SAE also must be reported to Pfizer Safety.

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 s/he 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 s/he determines that this drug did not cause the event, this should be clearly documented on the CRF and the NIS AEM Report Form.

10.4. Definitions of safety events

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. 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 dependency.

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 dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

- Test result is considered to be an AE by the investigator or sponsor.

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

Serious adverse events

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

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the 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 dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. 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 a medical floor, medical floor to a coronary care unit, 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 precipitating medical AE (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)

Scenarios necessitating reporting to Pfizer Safety 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).

For exposure during pregnancy in studies of pregnant women, data on the exposure to drug during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed, with the exception of those studies conducted in pregnant women (as described in above), for which data on the exposure are not reportable unless associated with serious or non-serious adverse events.

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 AEM 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 AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

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

Follow-up is conducted to obtain general information on the pregnancy; 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 can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, 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 investigational product.

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 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 accord 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 in the prescribing, dispensing, or administration of a medicinal product that 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 invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence 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, Extravasation

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

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence 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 reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

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 (http://www.info.pmda.go.jp)" as a listing of patients, which will include the names of drugs, adverse reactions, gender, 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. NAME, AND ADDRESS OF CONTRACTOR AS WELL AS SCOPE OF WORK CONTRACTED

- Company name: Pfizer R&D Japan
  Address: 3-22-7, Yoyogi, Shibuya-ku, Tokyo
  Scope of work contracted: Works related to planning of study, drafting of plan, implementation of study, monitoring, etc.

- Company name: Medidata Solutions
  Address: 2-7-2, Marunouchi, Chiyoda-ku, Tokyo
  Scope of work contracted: Establishment, operation and maintenance of the EDC system, etc.

- Company name: A2 Healthcare Corporation
  Address: 1-4-1, Koishikawa, Bunkyo-ku, Tokyo
  Scope of work contracted: Registration operations, etc.

- Company name: EPS Corporation
  Address: 2-23 Shimomiyabicho, Shinjuku-ku, Tokyo
  Scope of work contracted: Establishment of the EDC system, data management, statistical analysis, monitoring, etc.

13. 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.

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

- At the time of the report at 6 months after the start of the study or when the number of study subjects exceeds 1000, whichever comes first
- At the time of submission of periodic safety reports
- At the time of the final report

To comprehensively examine safety information, etc.

15. OTHER NECESSARY MATTERS

1. Amendment of the full protocol

Based on new findings obtained according to the progress of this study, the necessity of amendment of the full protocol will be examined and the full protocol will be amended as necessary. Also, the need for amendment of the full protocol will be examined and the full protocol will be amended when the partial change in the dosage and administration or indication is approved during the reexamination period (except when the reexamination period is newly designated), etc.

2. Actions to be taken for any problem or issue

Revision of the package insert and conduct of a new Post-marketing surveillance or new Post-marketing Clinical Trial should be considered for the following cases: any serious and unknown adverse reaction is suggested; a significant increase in the frequency of adverse reactions; any effectiveness or safety concern compared to pre-approval; rare adverse reaction is suggested.

16. CONTACT INFORMATION

16.1. Contact information for inquiries about the study

Name	PMS Affairs, Pfizer R&D Japan
Address	Shinjuku Bunka Quint Building, 3-22-7, Yoyogi, Shibuya-ku, Tokyo 151-8589
FAX	03-5309-9186
E-mail address	PAX_DRPMS@pfizer.com

16.2. Contact information for inquiries about the EDC system (In the case of study using EDC)

Name	Medidata Helpdesk
Business Hours	Weekdays: 9:00 - 20:00 (excluding Saturday/Sunday, Holidays and New Year Holidays)
TEL	PPD (Dedicated dial for Pfizer)
E-mail address	japanhelpdesk@mdsol.com

17. REFERENCES

Clinical Practice Guidance for New Coronavirus Infection COVID-19 Version 6.2 (27 January 2022)

18. LIST OF TABLES

19. LIST OF FIGURES

Not applicable

ATTACHMENT 1. TABLE OF CONTENTS OF INDEPENDENT DOCUMENTS

Not applicable

ATTACHMENT 2. ADDITIONAL INFORMATION

Not applicable