(Appendix)

Infliximab BS for Intravenous Drip Infusion 100 mg "Pfizer"

General investigation

(Psoriasis Vulgaris, Psoriasis Arthropathica, Pustular Psoriasis, or Erythrodermic Psoriasis)

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Pfizer Japan Inc.

STUDY INFORMATION

Title	Infliximab BS for Intravenous Drip Infusion 100 mg "Pfizer" Drug Use Investigation (Psoriasis Vulgaris, Psoriasis Arthropathica, Pustular Psoriasis, or Erythrodermic Psoriasis)
Protocol number	B5371009
Protocol version identifier	Version 8
Date	18 October 2022
Active substance	Infliximab (genetical recombination) [infliximab biosimilar 3]
Medicinal product	Infliximab BS for Intravenous Drip Infusion 100 mg "Pfizer"
Research question and objectives	To collect information on the safety and effectiveness of Infliximab BS for Intravenous Drip Infusion 100 mg "Pfizer" against psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis under actual status of use.
Author	PMS Planning & Operations Group 2, PMS Affairs PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
BSA	Body surface area involvement
CRP	C-reactive protein
CT	Computed Tomography
DAS	Disease Activity Score
EDC	Electronic Data Capture
NA	Not applicable
PASI	Psoriasis Area and Severity Index
VAS	Visual Analogue Scale

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 7	October 18, 2022	• Study information • Section 16.1	• Change of department name of author • Change of department name	• Due to change of organization
		• Section 5 • Section 8.10 • Section 9.4 • Section 12	• Addition of items • Change of terms • Adjustment of description • Adjustment of description	• Because the standard template was revised
		• Section 6	• Change of ministerial ordinances	• Due to partial revision of ministerial ordinances
		• Section 8.3.9 and 10	• Change of terms, etc.	• Due to change of internal form
		• Previous section 12	• Deletion, and all subsequent section numbers have been revised	• Amendment associated with the notification “Planning and publication of Risk Management Plan” dated 18 March 2022
		• Section 12	• Addition of work contracted	• Due to expansion of scope of work contracted
		• Section 16.2	• Change of contact information	• Due to change of contact information
Amended 6	October 22, 2021	• Section numbers • Section 8.7.9	• The table of contents has been renumbered to 1, and all section numbers have been revised • Editing the descriptions of the confirmation method for all patients registration	• Because the standard template was revised • To specify the confirmation method
Amended 5	September 17, 2021	• Study information	• Change of author • Adjustment of description	• Due to change of author

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		• Sections 1, 7.8.2.2 and 16.2 • Section 4 • Section 7.2.3 • General	• Change of End of data collection and Final study report • Change of Registration period and Investigation study period • Editing of descriptions associated with revision of the standard template	• Adjustment of description • Due to extension of the Registration period and Investigation study period • Due to extension of the Registration period and Investigation study period • Because the standard template was revised
Amended 4	May 30, 2019	• Section 9 • Section 16.2 • General	• Change of terms • Change of e-mail address for inquiries • Standardization of expressions	• Due to change of internal form • Due to change of e-mail address • Adjustment of description
Amended 3	February 15, 2019	• Sections 4	• Change in investigation schedule	• The date of preparation of the final report was changed.
Amended 2	January 10 , 2019	• Sections 4 and 7.2.3 • Sections 8.1 and 8.2 • General	• Change in investigation schedule • Description of obtaining informed consent from patients to be surveyed regarding disclosure, publication, etc. of survey results • Editing of descriptions associated with revision of the standard template	• Due to revision of the protocol • Because it was decided to obtain consent from the patients to be surveyed regarding the use of investigation results for other purposes. • Because the standard template was revised.
Amended 1	December 1, 2018	• Section 13 • Section 17.1	• Contractor was added • Change in the name of the contact	Establishment of Pfizer R&D Japan
Final	July 31, 2018	NA	NA	NA

5. MILESTONES

Milestone	Planned date
Start of investigation period	February 2019
Start of data collection (registration date for the first registered patient)	21 October 2019
End of investigation period	August 2024
End of data collection (date of database release)	12 March 2025
Final study report	September 2025

6. RATIONALE AND BACKGROUND

Infliximab BS for Intravenous Drip Infusion 100 mg "Pfizer" (generic name, infliximab [genetical recombination] [infliximab biosimilar 3]) (hereinafter, this drug) is a drug developed by Pfizer as a biosimilar of the original biopharmaceutical Remicade (the generic name and brand name of the product approved in Japan are infliximab [genetical recombination] and Remicade® for Intravenous Drip Infusion 100, respectively).

In Infliximab BS for Intravenous Drip Infusion 100 mg "Pfizer" Drug Use Investigation (Psoriasis Vulgaris, Psoriasis Arthropathica, Pustular Psoriasis, or Erythrodermic Psoriasis) (hereinafter, this study), information of the safety and effectiveness of this drug against psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis under actual status of use will be collected.

This study shall be conducted in strict compliance with the following ministerial ordinances and notifications:

- "MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171, dated December 20, 2004)
- "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)
- "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 on the 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)
- "Announcement of the MHLW Ordinance on the Partially Amend the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products (related to 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 collect information on the safety and effectiveness of this drug against psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis under actual status of use.

7.1. Safety specifications

[Important Identified Risks]

- Delayed-type hypersensitivity
- Lupus-like syndrome associated with seroconversion of anti-dsDNA antibody
- Demyelinating disease
- Hepatic impairment
- Serious infusion reaction
- Rhabdomyolysis
- Reactivation of hepatitis B
- Antibody production

[Important Potential Risks]

- Infection due to inoculation of live vaccines in children

8. RESEARCH METHODS

8.1. Study design

This study is a multi-center cohort study of patients with psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis receiving this drug. The investigators complete the case report form (CRF) based on the medical record containing data obtained in daily medical practice.

8.2. Setting

Patients meeting the registration conditions will be included in this study.

8.2.1. Registration criteria

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

1. Patients with psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis who started treatment with this drug

2. Patients who received this drug for the first time at the medical institution after the day of launch of this drug.

See the latest package insert in administering this drug.

8.2.2. Study sites

Conduct the study at 50 to 100 sites including the Department of Dermatology, Department of Orthopedic Surgery, etc.

8.2.3. Planned study period

The planned period covered by this investigation is as follows.

Investigation study: February 2019 to August 2024 (start of registration to completion of observation of the last registered patient)

Registration period: February 2019 to January 2024

8.2.4. Study procedures

8.2.4.1. Study method

This study will be conducted with all-case investigation system in patients with psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis.

This study will be conducted in patients who used this drug after the day of approval of dosage and administration for psoriasis at contracted medical institutions. Patients who used this drug before conclusion of the contract with the medical institution will also be included in this study (retrospective patients will be included).

8.2.5. Observation period

The observation period is 30 weeks* from the day of initial dose of this drug (Day 1). Information up to the day of visit immediately after 8 weeks have elapsed since the last dose during the observation period (day of study completion) will be collected in this study.

*: The period of 30 weeks is defined as up to Day 217 in consideration for allowance in visit days that occur in daily medical practice.

8.3. Variables

This study will be conducted in accordance with the observation schedule in Table 1.

Table 1. Variables and Schedule of observation

Timing / Variables		Registration form	CRF	
		At registration	At commencement of treatment	From commencement of treatment to day of study completion
Patient demographics	Identification number	●		
	Gender	●	●	
	Month of birth (or age at commencement of treatment with this drug)	●	●	
	Date of commencement of treatment with this drug	●		
	Check of registration conditions, target disease	●		
	Height		●	
	Weight		●	
	Target disease, duration of illness		●	
	Presence or absence and results of tuberculosis screening test, and record of administration of antituberculosis drugs		●	
	Presence or absence and results of hepatitis B virus test and hepatitis C virus test		●	
	Smoking history		●	
	Family history of malignant tumors (including lymphoma)		●	
	Medical history (past history and complications) (including the presence or absence of allergic history and hepatic impairment)		●	
	Presence or absence and duration of past use of infliximab preparations		●	
Prior and concomitant medications			●	●
Non-drug therapies			●	●
Record of administration of this drug			●	●*
Tests			●	●
Effectiveness evaluation Observation items: Skin findings and area of foci, and percentage of eruption to body surface area			●	●

Effectiveness evaluation (psoriasis arthropathica only) Observation items: Number of tender joints, number of swollen joints, patient's assessment of overall activity (patient VAS), and C-reactive protein (CRP)		●	●
Effectiveness evaluation (pustular psoriasis only) Observation item: Global improvement			●
Presence or absence of pregnancy (women only)		●	●
Confirmation of the day of study completion and administration status			●
Adverse events		●	●

*: Information on the use of this drug from the day of initial dose to the last dose during the observation period (30 weeks) will be collected.

8.3.1. Patient characteristics

Information at commencement of treatment with this drug will be entered in the registration form.

1. Identification number
2. Gender
3. Month of birth (or age at commencement of treatment with this drug)
4. Date of commencement of treatment with this drug
5. Check of registration conditions, target disease (psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis)

The following information at commencement of treatment with this drug will be entered in the CRF.

1. Height (cm)
2. Weight (kg)
3. Gender
4. Month of birth (or age at commencement of treatment with this drug)
5. Target disease (psoriasis vulgaris, psoriasis arthropathica, pustular psoriasis, or erythrodermic psoriasis), duration of illness (date of diagnosis)
6. Presence or absence and results of tuberculosis screening test (diagnostic imaging/tuberculin reaction test/interferon γ release test [QuantiFeron Test, T spot test, etc.]) and record of administration of antituberculosis drugs
7. Presence or absence and results of hepatitis B virus test and hepatitis C virus test (HBs antigen, HBs antibody, HBc antibody, and HCV antibody)

8. Smoking history
9. Family history of malignant tumors (including lymphoma)
10. Medical history (past history and complications) (including the presence or absence of allergic history and hepatic impairment)
11. Presence or absence and duration of past use of infliximab preparations

8.3.2. Prior and concomitant medications

8.3.2.1. Drugs used to treat psoriasis

The following information will be entered for drugs used to treat psoriasis immediately before the initial dose of this drug and concomitant medications used to treat psoriasis between the day of initial dose of this drug and the day of study completion.

1. Name of drug (product name)
2. Route of administration
3. Period of administration
4. Reason for discontinuation (inadequate effectiveness/adverse event/others)

8.3.2.2. Drugs used to prevent infection (including vaccines)

The following information will be entered for drugs used to prevent infection (including vaccines) between 6 months before the day of initial dose of this drug and the day of study completion.

1. Name of drug (product name)
2. Route of administration
3. Period of administration
4. Total daily dose and frequency of administration
5. Target of prophylactic administration

8.3.2.3. Drugs used to prevent infusion reaction

The following information will be entered for drugs used to prevent infusion reaction from before the initial dose of this drug to the day of study completion.

1. Name of drug (product name)
2. Route of administration

3. Period of administration

4. Total daily dose and frequency of administration

8.3.2.4. Drugs used to treat adverse events

The following information will be entered for drugs used to treat adverse events between the day of initial dose of this drug and the day of study completion.

1. Name of drug (product name)

2. Route of administration

3. Period of administration

8.3.3. Non-drug therapies

8.3.3.1. Non-drug therapies to treat psoriasis

The following information will be entered for non-drug therapies performed to treat psoriasis between 6 months before the day of initial dose of this drug and the day of study completion.

1. Name of therapy (name of procedure for surgery, etc.)

2. Period of implementation

8.3.3.2. Non-drug therapies to treat adverse events

The following information will be entered for non-drug therapies performed to treat adverse events between the day of initial dose of this drug and the day of study completion.

1. Name of therapy (name of procedure for surgery, etc.)

2. Period of implementation

8.3.4. Targeted drug use record

The following information will be entered for the status of use of this drug between the day of initial dose of this drug and the last dose during the observation period (30 weeks).

1. Dose

2. Weight

3. Date of administration

4. Reason for change

8.3.5. Tests

The results of tests performed between 3 months before the day of initial dose of this drug and the day of study completion will be entered.

1. Presence or absence of chest X-ray or chest CT, and presence or absence of abnormal findings
2. Laboratory tests: KL-6 and β-D-glucan (measured ranges and site reference ranges)

8.3.6. Clinical evaluation of effectiveness

Effectiveness will be evaluated based on the results of the following observation items.

8.3.6.1. Observation items

The results of the following items from before the initial dose of this drug (including the day of initial dose) to the day of study completion will be entered.

8.3.6.1.1. Observation items for psoriasis vulgaris, pustular psoriasis, or erythrodermic psoriasis

1. Skin findings (erythema, infiltration/thickening, and scale) and area of foci
2. Percentage of eruption to body surface area

8.3.6.1.2. Observation items for psoriasis arthropathica

1. Skin findings (erythema, infiltration/thickening, and scale) and area of foci
2. Percentage of eruption to body surface area
3. Number of tender joints (assessment of 28 joints)
4. Number of swollen joints (assessment of 28 joints)
5. Patient's assessment of overall activity (patient VAS)
6. C-reactive protein (CRP)

8.3.6.2. Effectiveness evaluation scale for each disease

8.3.6.2.1. Effectiveness evaluation scale for psoriasis vulgaris or erythrodermic psoriasis

The following will be calculated based on information collected for observation items to evaluate effectiveness.

- Psoriasis area and severity index (PASI) score
- BSA (Body surface area involvement)

8.3.6.2.2. Effectiveness evaluation scale for psoriasis arthropathica

For psoriasis arthropathica, the following will be calculated based on information collected for observation items in addition to PASI score and BSA to evaluate disease activity.

- Disease Activity Score (DAS) 28

8.3.6.2.3. Effectiveness evaluation scale for pustular psoriasis

For pustular psoriasis, the following assessment by the investigator will be evaluated in addition to PASI score and BSA.

- Global improvement

8.3.7. Presence or absence of pregnancy (women only)

The presence or absence of pregnancy between the day of initial dose of this drug and the day of study completion will be entered.

8.3.8. Confirmation of the day of study completion and administration status

The following information will be entered as to whether treatment with this drug is ongoing on the day of study completion.

1. Date of study completion
2. Whether treatment is ongoing
3. Reason for discontinuation (completion) (choose from the following)
    a. Remitted (symptom improved)
    b. Inadequate clinical effect
    c. Adverse event (enter necessary information in the adverse event column)
    d. No revisit
    e. Others (enter reasons for discontinuation)

8.3.9. Adverse events

An Adverse Event (AE) is any untoward medical occurrence in a patient administered a medicinal product.

Occurrence of adverse events 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.

1. Presence/absence of adverse events
2. Name of adverse event
3. Category of adverse event (whether it falls under infusion reaction and timing of onset)
4. Date of occurrence
5. Intervention
6. Seriousness
7. Outcome
8. Date of outcome
9. Causal relationship

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

10. Presence or absence of tests related to adverse events
11. Date of test
12. Name of test
13. Site reference value
14. Unit
15. Results

8.4. Adverse events of note

Adverse events of note in this study are shown below.

Serious infection (pneumonia, Pneumocystis pneumonia, sepsis, opportunistic infection, etc.), tuberculosis, delayed-type hypersensitivity, serious blood disorder, lupus-like syndrome associated with seroconversion of anti-dsDNA antibody, demyelinating disease, hepatic impairment, serious infusion reaction, interstitial pneumonia, rhabdomyolysis, reactivation of hepatitis B, antibody production, malignant tumor, and infection due to inoculation of live vaccines in children

8.5. Data sources

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

8.6. Study size

8.6.1. Planned sample size

Target sample size is to be 100 subjects for safety analysis (At least 50 patients with psoriasis vulgaris and at least 5 patients with psoriasis arthropathica. Patients with pustular psoriasis and erythrodermic psoriasis will be collected as much as possible.)

If the target sample size is not reached at completion of the registration period, Sponsor will discuss measures with PMDA.

8.6.2. Rationale for sample size

The target sample size was set at 100 taking the feasibility of the study into consideration.

The data collected from 100 subjects to whom this drug is administered should enable to detect and verify, with a probability of 95%, at least 1 subject in whom each adverse event with an incidence of 3% or more occurs.

8.7. Data management

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

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

A CRF is required and should be completed for each included 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 and/or paper 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 with 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.

8.7.2. 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.

8.7.3. Data collection method (EDC)

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

8.7.4. Patient registration (EDC)

After conclusion of the contract, target patients will be promptly registered. If an unregistered patient is found during the registration period, the patient will be promptly registered. All patients confirmed to have received this drug will be registered because this study will be conducted using all-case investigation system.

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

If there is something to be confirmed found in the registration form, confirmation will be requested with the investigator. Registration will be fixed after the confirmation.

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

8.7.5.1. Data entry

The investigator shall, upon confirming the study items, input the data in this system based on medical charts, and save the data.

8.7.5.2. Data revision

Upon receiving Sponsor's inquiry on the contents of the CRF (query forms), the investigator will again confirm the contents of medical records, and as required, correct relevant sections and save the data.

8.7.5.3. Submission

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

8.7.6. Data collection method (paper CRFs)

In this study, the data will be collected and confirmed by using paper CRFs, only when the EDC is not available at the study sites.

8.7.7. Patient registration (paper CRFs)

After conclusion of the contract, target patients will be promptly registered. If an unregistered patient is found during the registration period, the patient will be promptly registered. All patients confirmed to have received this drug will be registered because this study will be conducted using all-case investigation system.

The investigator will complete the “registration form” provided by Sponsor for patients who received this drug and fax it to the toll-free number specified in the registration form.

【Patient Registration Center】
FAX：0120‐508‐123（Available 24 Hours）
Business hours：9:00～17:15*（except for Saturdays, Sundays, National Holidays, and New Year Holidays）
*：FAX transmission after 15:15 will be responded during the following business day.

1. After the patient was registered, “the announcement of the patient registration” will be sent by FAX. Investigator will save the announcement in the site.

2. If there is something to be confirmed found in the registration form, confirmation will be requested with the investigator. In the case of confirmation, “request form of confirmation” and “registration form (copy)” will be sent from the Registration Center to the investigator by FAX.

8.7.8. Points to consider for completion, revision, and submission of case report form (paper CRFs)

8.7.8.1. Data entry

The investigator shall, upon confirming the study items, complete the CRF based on medical charts and other medical records such as relevant test results, using an ineffaceable ink such as ballpoint pen.

8.7.8.2. Data revision

Upon receiving Sponsor's inquiry on the contents of the CRF (query forms), the investigator will again confirm the contents of medical records described earlier, and as required, correct relevant sections and resubmit the form.

8.7.8.3. Submission

CRFs should be submitted promptly upon completion in accordance with the procedures set out by Sponsor.

8.7.9. All cases survey registration

1. Periodically, investigator will confirm whether all patients registered are recorded on “the list of patients registered in this study” or not, provide signature (or putting down the investigator’s name and putting investigator’s seal on), and submit the list to the site staff. However, if the medical institution has established restrictions on visits, etc., an alternative method such as e-mail should be used.

2. If the unregistered patients were found, investigator will register the patient at once.

8.8. Data analysis

8.8.1. Definition of analysis set

The safety analysis set (SAS) will be a full analysis set (FAS) that is as closer as possible to all patients who received this drug. The effectiveness analysis set will be a set of patients for whom the effectiveness evaluation is considered possible among the safety analysis set according to the separately prescribed Statistical Analysis Plan (SAP).

8.8.2. Method of analysis

8.8.2.1. Analysis for safety evaluation

The onset of major adverse reactions and incidence of adverse reactions (percentage of patients with adverse events for which the causal relationship with this drug cannot be ruled out) in the SAS will be analyzed. In addition, patient demographics and incidence will be tabulated for infusion reaction, hypersensitivity, and hepatic impairment in the SAS, and these events will be evaluated in terms of seriousness and whether treatment was required.

8.8.2.2. Analysis for effectiveness evaluation

Values before and after administration of this drug will be summarized for effectiveness endpoints based on PASI score, BSA, and DAS28.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (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.

8.9. 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 charts.

8.10. Limitations of the research methods

There may be potential limitations in this study:

- 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.
- Due consideration may not be given to confounding factors due to insufficient background information collected.
- Since this study collects the information described in medical charts, specified data may not be collected or may be missing.

8.11. 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 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 Ordinance 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

The table below summarizes the requirements for recording safety events on the CRF 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 56 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 56 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

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. 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.

10.4.2. 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)

10.4.3. 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 and monitoring, etc.

Company name: Medidata Solutions
Address: 2-7-2 Marunouchi, Chiyoda-ku, Tokyo
Scope of work contracted: Construction of EDC, duties related to administration, etc.

Company name: A2 Healthcare Corporation
Address: 1-4-1 Koishikawa, Bunkyo-ku, Tokyo
Scope of work contracted: Contract duties, reception of registration form, delivery and receipt of CRF, etc.

Company name: EPS Corporation
Address: 2-23 Shimomiyabicho, Shinjuku-ku, Tokyo
Scope of work contracted: Construction of EDC, data management duties, analysis duties

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.

- Review the necessity for changing the contents of risk minimization activities for the current safety specifications.

- 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.).

- 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

Review and report the safety every year from approval to submission of the final report.

15. OTHER NECESSARY MATTERS

15.1. Amendment of the Study Protocol

Based on the new knowledge to be obtained according to the progress of this study, the need for amendment of the protocol will be examined and the Study Protocol will be amended if necessary. Also, the need for amendment of the Study Protocol will be examined and the 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.

15.2. 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
E-mail address	IFX_PMS@pfizer.com

16.2. Contact information for inquiries about the EDC system

Name	Medidata Helpdesk

Business Hours	Weekday 9:00-20:00 (excluding Saturdays, Sundays and holidays, Year-end and New Year holidays)
TEL	0800-222-2099 (dedicated to Pfizer)
E-mail address	japanhelpdesk@mdsol.com

17. REFERENCES

Not applicable

18. LIST OF TABLES

19. LIST OF FIGURES

Not applicable

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable

ANNEX 2. ADDITIONAL INFORMATION

Not applicable

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