(Annex)

TRASTUZUMAB BS for Intravenous Infusion 60 mg [Pfizer]

TRASTUZUMAB BS for Intravenous Infusion 150 mg [Pfizer]

General Investigation

(Unresectable Advanced/Recurrent HER2-Overexpressing Gastric Cancer)

Full Protocol

Pfizer Japan Inc.

STUDY INFORMATION

Title	TRASTUZUMAB BS for Intravenous Infusion 60 mg [Pfizer]/TRASTUZUMAB BS for Intravenous Infusion 150 mg [Pfizer] General Investigation (Unresectable Advanced/Recurrent HER2-Overexpressing Gastric Cancer)
Protocol number	B3271007
Proto version identifier	Version 5
Date	22 December 2022
Generic name	Trastuzumab (Genetical Recombination) [Trastuzumab Biosimilar 3]
Product name	TRASTUZUMAB BS for Intravenous Infusion 60 mg [Pfizer]/TRASTUZUMAB BS for Intravenous Infusion 150 mg [Pfizer]
Research question and objectives	To confirm the safety and efficacy of this drug under the actual use.
Author	PPD

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
CA19-9	Carbohydrate antigen19-9
CEA	Carcinoembryonic antigen
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	Electronic Data Capture
HER2	Human Epidermal growth factor Receptor Type 2
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LVEF	Left ventricular ejection fraction
MUGA	Multiple-gated acquisition technique
NE	Not Evaluable
PD	Progressive Disease
PR	Percial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable Disease
SAP	Statistical Analysis Plan

2. RESPONSIBLE PARTIES

The Japan Good Post marketing Study Practice officer

3. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Amended 4	22 December 2022	Cover page	Change of the company logo	Change of the logo
		STUDY INFORMATION	Change of the department of the author	Organizational change
		4., 7.6.1., 7.6.5., 7.9., 8.4.	Addition of items and updates of descriptions	Adjustment of description
		5	Updates of ministerial ordinance, notification, etc.	Partial amendment to the ministerial ordinance

		9., 9.4.1., 9.5.	Changes of Japanese translation and adjustment of description	Changes associated with revision of the internal format
		Former 11	Deletion (moving up the following numbers)	Adjustment of description associated with the notification of "Establishment and Publication of Risk Management Plan" dated March 18, 2022
		11.	Updates of the scope of contracted work and adjustment of description	Expansion of the scope of contracted work
		15.1.	Change of the department name in contact information and adjustment of description	Organizational change
		15.2.	Change of the telephone number in contact information and adjustment of description	Change of the phone number in contact information
		17	Update of the relevant page	Adjustment of description
Amended 3	31 May 2021	STUDY INFORMATION	Changes of version identifier, date of preparation, and author	Change of version identifier and person in charge
		4. MILESTONES	Clarification of the date of start of the study Change of the date of study completion/date of preparation of final	Because the timing of the start of the study became clear Prolongation of the investigation

			report	period
		7.2.4. Planned study period	Change of the investigation period/registration period	Prolongation of the investigation period/registration period
Amended 2	24 June 2019	7.6.4. Patient Registration (EDC)	Description of the period of patient registration	Setting of the registration period as a mandatory procedure
Amended 1	24 May 2019	STUDY INFORMATION	Change of responsible personnel	Adjustment of description associated with revision of internal standard forms
		9	Addition of the section for management and reporting of adverse events/adverse reactions	
		Cover page, etc.	Correction of terms	
Initial	28 March 2019	N/A	N/A	N/A

4. MILESTONES

Milestone	Planned date
Start of the study	August 2019
Start of data collection (registration of the first patient)	Around August 2023
Completion of the study	February 2025
End of data collection (release of the database)	Around September 2025
Final study report	Within 7 years after the start of marketing

5. RATIONALE AND BACKGROUND

TRASTUZUMAB BS for Intravenous Infusion 60 mg [Pfizer] and TRASTUZUMAB BS for Intravenous Infusion 150 mg [Pfizer] (generic name: trastuzumab [genetical recombination] [Trastuzumab Biosimilar 3]) (hereinafter referred to as this drug) are biosimilar products of the biologic product Herceptin (the generic name of the product approved in Japan: trastuzumab [genetical recombination], and the product name: HERCEPTIN for Injection 60 and HERCEPTIN for Injection 150).

This general investigation (hereinafter, this study) is intended to investigate the safety and efficacy of this drug under the actual use in patients with unresectable advanced/recurrent gastric cancer with HER2 overexpression.

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

6. RESEARCH QUESTION AND OBJECTIVES

To confirm the safety and efficacy of this drug under the actual use.

6.1. Safety Specifications

[Important Identified Risks]

- Cardiac disorder
- Infusion reactions
- Haematotoxicity
- Interstitial pneumonia/lung disorder
- Hepatic failure/liver disorder
- Coma, cerebrovascular disorder, brain oedema
- Renal disorder
- Infection
- Tumour lysis syndrome

7. RESEARCH METHODS

7.1. Study Design

This study is an open-label, multicenter, one arm prospective observational cohort study in patients with unresectable advanced/recurrent gastric cancer who have been confirmed to have HER2 overexpression receiving this drug. The investigators complete the case report form (CRF) based on the information extracted from the medical record created in daily medical practice.

7.2. Setting

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

7.2.1. Registration criteria

Patients who meet all of the following registration criteria to be eligible for inclusion in this study.

1. Patients with unresectable advanced/recurrent gastric cancer who are confirmed to have HER2 overexpression and started treatment with this drug*
2. Patients who receive this drug* for the first time after this drug* is launched

Refer to the latest package insert of this drug when this drug is administered.

* Not including the biological product, HERCEPTIN, and biosimilars of HERCEPTIN other than this drug

7.2.2. Exclusion criteria

Exclusion criteria are not specified in this study.

7.2.3. Study sites

The survey will be conducted at approximately 50 medical institutions including the department of medical oncology, the department of surgical oncology, the department of gastrointestinal surgery, and the department of gastrointestinal medicine.

7.2.4. Planned study period

The planned period of covered by this study is as follows.

Investigation period: August 2019 to February 2025 (from the start of the registration period to the completion of the observation period of the last patient)

Registration period: August 2019 to August 2024

7.2.5. Study procedures

7.2.5.1. Study method

Central registration system: Patients meeting the registration criteria will be registered until data are collected on a target number of patients.

7.2.6. Observation period

The start of observation is defined as the first date of the administration of this drug (Day 1), and the observation period lasts until 28 days after the last dose within 24 weeks from the start of administration, the first dose of this drug administered more than 24 weeks after the start of administration, or the start of the next treatment, whichever comes first.
However, if administration of this drug is discontinued in earlier than 24 weeks, the observation period will be until 28 days after the date of discontinuation of this drug or the start of the next treatment, whichever comes first.

7.3. Variables

This study will be conducted according to the observation schedule in Table 1.

Table 1. Variables and schedule of observation

Variable	Registration form	Case report form
	At registration	Observation period Until 24 weeks from the start of administration*
ID number	●	○
Gender	●	○
Year of birth	●	○
Date of the start of administration of this drug	●	○
Confirmation of eligibility	●	
Informed consent		●
Body weight		●
Disease, disease stage, lesion site, date of initial diagnosis of gastric cancer		●
Family history of malignancy		●
Medical history		●
Presence/absence of history of trastuzumab products use, drug name, target disease		●
Previous treatment drugs/concomitant medications		●
Non-drug therapy		●
Targeted drug use record		●
Tests		●
ECOG PS		●
Effectiveness evaluation		●
Pregnancy (Female Only)		●
Records of continuation/discontinuation (completion) of study and completion of observation		●
Adverse events		●

○: Some elements in the Registration Form are automatically reflected in the CRF. Investigators should check and update the CRF as needed.
*: If administration of this drug is discontinued in earlier than 24 weeks, the observation period will be until 28 days after the date of discontinuation of this drug or the start of the next treatment, whichever comes first. Information before the start of administration is included depending on the variables.

7.3.1. Patient characteristics

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

1. ID number
2. Gender
3. Year of birth
4. Date of the start of administration of this drug
5. Confirmation of eligibility

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

1. ID number
2. Gender
3. Year of birth
4. Informed consent
5. Body weight
6. Disease (unresectable advanced/recurrent HER2-overexpressing gastric cancer), disease stage (TNM), lesion site (peritoneum, lymph node, liver, others), and date of initial diagnosis of gastric cancer
7. Family history of malignancy
8. Medical history (past history and concurrent illness) (including history of allergy and presence or absence of hepatic function disorder)
9. Presence/absence of history of trastuzumab products use,* drug name, target disease (advanced/recurrent gastric cancer, breast cancer, and others)

* The biological product, HERCEPTIN, and biosimilars of HERCEPTIN other than this drug

7.3.2. Administration record of targeted drug

The following information will be recorded regarding the status of use of this drug from the date of the start of administration of this drug to the date of the end of the observation period.

1. Dose per administration
2. Date of administration
3. Reason for use (first-line therapy, second-line therapy, and others)
4. Reason for change (adverse events [AEs], change to maintenance dose, and others)

7.3.3. Prior therapy (drug therapy)

Enter the information on previous treatment drugs used for the treatment of unresectable advanced/recurrent HER2-overexpressing gastric cancer before the start of administration of this drug. However, the drugs that are continuously used even after the start of administration of this drug should be entered in concomitant therapy (drug therapy).

1. Drug name
2. Route of administration
3. Reason for discontinuation (in the case of discontinuation) (inadequate response, AEs, and others)

7.3.4. Concomitant therapy (drug therapy)

Enter the following information on the drugs used for the treatment of unresectable advanced/recurrent HER2-overexpressing gastric cancer from the date of the start of treatment with this drug to the date of the end of the observation period.

1. Drug name
2. Route of administration
3. Date of the start of administration and date of the end of administration

7.3.5. Concomitant therapy (non-drug therapy)

Enter the following information on the non-drug therapies conducted for the treatment of unresectable advanced/recurrent HER2-overexpressing gastric cancer between 6 months before the date of the start of administration of this drug and the date of the end of the observation period.

1. Name of therapy (name of surgical procedure for surgery, etc.)
2. Start date and end date

7.3.6. Drugs used for prevention of infusion reactions

Enter the following information on drugs used for prevention of infusion reactions caused by administration of this drug.

1. Drug name
2. Route of administration
3. Date of administration

7.3.7. Tests

7.3.7.1. Clinical laboratory tests

Enter all of the results of tests performed at baseline (the most recent data from 3 months before the date of the start of administration of this drug to the day before the start of administration of this drug) and during the observation period.

Clinical laboratory tests: CEA, CA19-9, QT, QTc, LVEF (echocardiogram or MUGA scan)

7.3.8. ECOG PS (Eastern Cooperative Oncology Group Performance Status)

Enter the data at baseline (the most recent data from 3 months before the date of the start of administration of this drug to the day before the start of administration of this drug) and at the end of administration (the most recent data before the end of the observation period).

1. Date of evaluation

2. Evaluation results

7.3.9. Pregnancy (female only)

Enter the pregnancy status from the date of the start of administration of this drug to the date of the end of the observation period.

7.3.10. End-of-study (discontinuation record)

Enter the following information regarding whether or not treatment with this drug is continued at the end of the observation period.

1. Date of the end of the observation period/discontinuation
2. Reason for discontinuation (completion) (Select from the following.)
    a. Completed (treatment continued)
    b. Insufficient clinical effectiveness
    c. Adverse event (Enter necessary information in the column of AEs.)
    d. Death (Enter necessary information in the column of AEs.)
    e. No return visit
    f. Transfer to another hospital/department
    g. Others (Enter reason for discontinuation.)

7.3.11. Effectiveness evaluation

Enter the following items from baseline to the date of the end of the observation period. Enter the information as of the time of discontinuation if the administration of this drug is discontinued.

Evaluate the effectiveness of this drug using the effectiveness assessment items in "Guidelines on New Response Evaluation Criteria in Solid Tumors, version 1.1" and enter the results.

Assessment of tumor response: Assess the tumor response according to RECIST Ver. 1.1. Identify target lesions and non-target lesions in the classification of tumor lesions at the start of administration of this drug, and confirm the presence or absence of new lesions in addition to the results of assessment of tumor response in each tumor lesion during the observation period, and then evaluate overall response.

1. Presence or absence of target lesions at the start of administration of this drug
2. Presence or absence of effectiveness evaluation

- Date of assessment of best overall response

- Best overall response (CR, PR, SD, PD, NE, Non-CR/Non-PD)

7.3.12. Adverse events

Occurrence of AEs 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 AE
- Name of AE
- Classification of AE (presence/absence of infusion reactions)
- Date of occurrence
- Severity of AE (CTCAE Grade ver. 5.0)
- Intervention
- Change in administration of this drug
- Seriousness
- Outcome
- Date of resolution or recovery/date of death
- Date of outcome confirmation
- Causal relationship to this drug
- Most likely cause of AE

7.4. 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.

7.5. Study Size

7.5.1. Planned sample size

100 patients as the safety analysis set (SAS)[*1]

*1: The safety analysis set is defined as the full analysis set that is as close as possible to all patients treated with this drug.

7.5.2. Rationale for sample size

By accumulating data from 100 patients, it is possible to detect AEs with a true incidence of 3% or higher in at least 1 patient with a probability of approximately 95% in a general investigation.

7.6. Data Management

7.6.1. Case report form (CRF)/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 in 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 physician's medical records. In these cases, data collected on the CRFs must match those records.

7.6.2. 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.

7.6.3. 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, hereinafter referred to as EDC).

7.6.4. 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 within 27 days after the first administration of this drug.

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

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

7.6.5.1. Data entry

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

7.6.5.2. 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.

7.6.5.3. Submission

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

7.7. Data Analysis

1. Definition of analysis set

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

2. Method of analysis

- Analysis for safety evaluation

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

- Analysis for effectiveness evaluation

Analyses for effectiveness evaluation based on RECIST evaluation will be performed.

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

7.8. Quality Control

Prior to conducting the study, the personnel in charge of the study site will explain to the investigator about the contents of the Full Protocol, etc. and ask the investigator for completion of a CRF based on medical records.

7.9. Limitations of the Research Methods

There may be potential limitation 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 AEs 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 information described in medical records, specified data may not be collected or may be missing.

7.10. Other Aspects

Not applicable

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of data of patients 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 sites will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of a 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 study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his/her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient's personal data consistent with the clinical study agreement and applicable privacy laws (Personal Information Protection Law).

8.2. Patients Consent

In principle, the information provided to Pfizer in this study does not correspond to the personal information specified in the Personal Information Protection Law or is provided based on the laws and regulations (even if it corresponds to personal information under the Personal Information Protection Law). Therefore, it is not necessary to obtain the patient's consent to the provision of personal information from the study site to Pfizer. Similarly, it is not necessary to obtain informed consent from patients because reporting or submission of information and results obtained in this study from Pfizer to Japanese regulatory authorities or provision of information to healthcare professionals as necessary is based on the applicable laws and regulations.

In this study, Pfizer will collect information that cannot identify specific patients from the study sites. The results of this study, which are prepared not to identify specific patients, may be reported to Pfizer Inc. 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 Law, these actions may not be based on the laws or regulations, and therefore, may correspond to provision to the third party and using the information for purposes other than business that require consent from the patient. Therefore, the study sites will obtain written or verbal consent from the patients to be included in this study so that Pfizer can use the results of this study to report to Pfizer Inc., group companies or regulatory authorities in other countries, or to present it at academic conferences or publish manuscript, etc. Whether consent is obtained from patients or not is described in the CRF. The original of the written informed consent form should be retained by the study investigator.

In general, the investigator must obtain consent from a patient personally. However, if the investigator determines that a patient's decisional capacity is so limited that he/she cannot reasonably be consulted or he/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/her own consent, the source documents must record the relationship of the person signing the consent to the patient (e.g., parent(s), spouse). If a minor registered in the study reaches adulthood during the study, the consent will be acquired 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/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.

8.3. 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.

8.4. Ethical Conduct of the Study

This study will be conducted in compliance with the ministerial ordinances, etc. in "5. RATIONALE AND BACKGROUND," and will also be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

9.1. Requirements for Records and Reporting

The table below summarizes the requirements for recording safety events in 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 3 types of events: (1) serious AEs (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including drug exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section of "Definition of Safety Events."

Safety Event	Record on the CRF	Report events to Pfizer Safety within 24 Hours of Awareness using the NIS AE Report Form
Serious AEs	All	All
Non-serious AEs	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breastfeeding, 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 adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (See the section of "Serious Adverse Events" below).

The safety events for which reporting to Pfizer Safety is required in the table above must be reported to Pfizer Safety within 24 hours of awareness of the event by the investigator, **whether or not the investigator determines that the event is related to this drug.** In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available information. This timeframe also applies to additional new (follow-up) information on a previously forwarded 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 event.

For safety events that are considered serious or are specified in the far right column of the table above as requiring reporting to Pfizer Safety within 24 hours of awareness, the investigator must conduct follow-up and report any additional information to Pfizer Safety in accordance with the 24 hour timeframe. In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is required to be more detailed than the information recorded in the CRF. In general, this information will include a description of the event in sufficient detail to allow for a complete medical assessment of the AE and enabling independent determination of possible causality. Information on the event (concomitant drugs, complications, etc.) must also be provided. In the event of a patient's death, a summary of available autopsy findings must be promptly provided to Pfizer Safety or persons to whom Pfizer outsources such operations.

9.2. Reporting Period

The reporting period for each patient's safety event (see the table above) to Pfizer Safety begins with the first administration of this drug to the patient and ends at the end of the observation period for the survey, but is at least 28 days (calendar day) after the last dose of this drug. If safety events of the types listed in the table above occur during this reporting period, the investigator should submit a report to Pfizer Safety unit of Pfizer (or persons to whom Pfizer outsources such operations). If a patient is receiving this drug on the last day of the observation period, the reporting period should be extended to 28 days (calendar day) after the end of the observation period.
If the investigator learns of any SAE occurring at any time after completion of the survey and he/she considers the SAE to be related to this drug, the SAE should also be reported to Pfizer Safety.

9.3. Causality Assessment

The investigator must assess and record causality. In addition, the investigator should obtain sufficient information to determine the causal relationship of each AE. For AEs related to this drug, follow-up by the investigator is required until the event or its sequelae resolves, or stabilizes at a level acceptable to the investigator, and Pfizer agrees with that assessment.

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

If the investigator cannot identify the cause of the event, but determines that this drug does not cause the event, this should be clearly documented in the CRF and NIS AE Report Form.

9.4. Definition of Safety Events

9.4.1. Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event does not necessarily have a causal relationship with the administration or use of the product. Examples of AEs include, but are not limited to:

- Abnormal test findings (See below for conditions under which abnormal laboratory findings constitute an AE.);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

In addition, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breastfeeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal test finding should be reported as an AE are as follows:

- Test result is associated with accompanying any related symptoms;
- Test result requires additional diagnostic testing or medical/surgical intervention;
- Test result leads to a change in dosing of this drug, discontinuation of the study, or addition of concomitant drug treatment or other treatment;

- The investigator or Pfizer judges it to be an AE.

Continuation of an abnormal value that does not meet any of the above criteria is not an AE. Abnormal values due to laboratory errors do not need to be reported as AEs.

9.4.2. Serious adverse events

An SAE is any untoward medical occurrence in a patient who received a medicinal or nutritional product (including pediatric preparations) at any dose that:

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

Progression of the malignancy (including signs and symptoms of progression) investigated in this study shall not be reported as an SAE unless the outcome during the reporting period is death. Hospitalization for signs and symptoms of disease progression will not be reported as an SAE. However, if the outcome of the malignancy during the study or during the reporting period is death, the event leading to death must be recorded as an AE and must be reported as a Grade 5 SAE.

Medical and scientific judgment is exercised in deciding whether an event is a significant medical event. A significant 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 outcomes listed above, the significant event should be reported as an SAE.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasia or convulsion that do not result in hospitalization; or development of drug dependency or drug abuse.

In addition, suspected transmission of an infectious agent via a Pfizer product is considered serious, whether pathogenic or non-pathogenic. The event may be suspected based on clinical signs or laboratory findings suggestive of infection in patients exposed to a Pfizer product. The term "suspected transmission of infection" is considered synonymous with "infection transmission." These cases will be considered unexpected and will be handled as serious expedited cases by Pfizer Safety. Such cases should also be considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Hospitalization also includes transfer within the hospital to other department or the acute/intensive care unit (e.g., transfer from the psychiatric ward to a medical floor, from the medical floor to a coronary care unit, or from neurological floor to a tuberculosis unit, etc.). An emergency room visit does not necessarily constitute a hospitalization; however, events leading to the emergency room visit is assessed for medical significance.

Hospitalization without a medical AE is not in itself an AE, and reporting is not required. Followings are examples of hospitalization without medical AEs that does not need to be reported.

- Social hospitalization (e.g., no accommodation for patients/subjects)
- Administrative hospitalization (e.g., for annual medical checkup)
- Optional hospitalization not associated with a precipitating clinical deterioration (e.g., optional cosmetic surgery)
- Hospitalization for observation without a medical AE
- Hospitalization for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (e.g., close examination for a persistent pretreatment laboratory abnormality)

9.5. 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 directly exposed (e.g., environmental exposure) to this drug. A female becomes, or is found to be, pregnant after discontinuing or having been directly exposed to this drug (maternal exposure).

   Environmental exposure includes direct contact with a Pfizer product in a pregnant woman (for example, a nurse reports a pregnancy and has been exposed to chemotherapeutic products).

2. A male has been exposed to this drug prior to or around the time of conception by treatment or environmental exposure. A male has been exposed during his partner's pregnancy (paternal exposure).

For exposure during pregnancy in studies of pregnant women, data on the exposure to this 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 subject or a subject's partner becomes, or is found to be, pregnant during the course of treatment with this drug, this information must be submitted to Pfizer on the NIS AE Report Form and the EDP Supplemental Form, regardless of whether an AE has occurred.

In addition, information regarding environmental exposure of a pregnant woman to this drug (e.g., accidental aspiration of a cytotoxic agent by a pregnant subject or exposure to the spilled agent) must be submitted using the NIS AE Report Form and the EDP Supplemental Form. These reports must be made irrespective of whether an AE has occurred.

The information submitted should include the estimated date of delivery (See below for information on termination of pregnancy).

General information on pregnancy will be followed up. In addition, all EDP reports with unknown pregnancy outcome will be followed up for EDP outcome information. The pregnancy will be followed until birth or termination of the pregnancy (induced abortion, etc.) and the outcome will be reported to Pfizer. This information is provided as a follow-up to the initial EDP report. In the case of a newborn, the absence of external malformation in the newborn shall be evaluated at 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 the test confirms a congenital anomaly and is reported).

If the outcome of the pregnancy meets the criteria for an SAE (i.e. ectopic pregnancy, spontaneous abortion, intrauterine fetal death, neonatal death, 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 regarding pregnancy outcomes to be reported as SAE is provided below.

- Spontaneous abortion includes miscarriage and missed abortion.
- Neonatal deaths that occur within 1 month of birth should be reported as SAEs regardless of causality. 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 drug 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 recorded that this document was provided to the study participant, which was to be provided to the 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 drug exposure during breastfeeding.

Medication error

A medication error is any preventable event, which may lead to inappropriate use of a drug under the management of a healthcare professional, patient, or consumer, or may exert adverse effects on patients. Such events may be related to medical practices, products, procedures, and systems, including prescribing, prescription transmission, product labeling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use.

Examples of medication errors are as follows:

- Any medication errors prevented in advance regardless of whether having direct impacts on patients (e.g., inadvertent/incorrect administration where the healthcare professional or patient/consumer uses the product incorrectly at a dose or administration method not listed in the product label or prescription)
- Mix-up of name (e.g., product name)

The investigator must submit reports on the following medication errors with or without associated AEs/SAEs:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not directly involve the patient (potential medication errors or errors nearly missed, including the ones which are latent or prevented in advance). If the medication error does not involve patient exposure to the product, a medication error report will be generated based on the following minimum criteria:
  - Identifiable reporter
  - Suspected product

- Event of 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 accosiated 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 accosiated AE/SAE.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Information collected in this study will be used for reporting to the 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 reexamination (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" (Act 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.

11. NAME AND ADDRESS OF CONTRACTOR AS WELL AS SCOPE OF WORK CONTRACTED

Company name: Pfizer R&D Japan G.K.
Address: 3-22-7, Yoyogi, Shibuya-ku, Tokyo

Scope of work contracted: Works related to planning and drafting of study, operation of the study, and monitoring etc.

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

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

12. 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.

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

Safety review and reporting at the time of evaluation report and completion of the study.

14. OTHER NECESSARY MATTERS

1. Amendment of the Full Protocol

Based on the new knowledge to be obtained according to the progress of this study, the need for amendment of the Full Protocol will be examined and the Full Protocol will be amended if 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 in the case of 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.

15. CONTACT INFORMATION

15.1. Contact Information for Inquiries about the Study

Name	PMS Affairs, Pfizer R&D Japan G.K.
Address	3-22-7, Yoyogi, Shibuya-ku, Tokyo, 151-8589
Fax number	03-5309-9186
E-mail address	TSX_DRPMS@pfizer.com

15.2. Contact Information for Inquiries about Post-marketing Surveillance Data Collection System

Name	Medidata Helpdesk
Business Hours	Weekdays: 9:00 to 20:00 (excluding Saturdays, Sundays, national holidays and year-end and beginning)
TEL	PPD (exclusive number for Pfizer)
E-mail address	japanhelpdesk@mdsol.com

16. REFERENCES

Not applicable

17. LIST OF TABLES

18. LIST OF FIGURES

Not applicable

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable

ANNEX 2. ADDITIONAL INFORMATION

Not applicable

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