(Appendix)

Special investigation for VIZIMPRO Tablets

FULL PROTOCOL

Pfizer Japan Inc.

STUDY INFORMATION

Title	Special investigation for VIZIMPRO Tablets
Protocol number	A7471048
Protocol version identifier	Amended 5
Date	18 July 2024
Active substance	Dacomitinib hydrate
Medicinal product	VIZIMPRO Tablets 15 mg/VIZIMPRO Tablets 45 mg
Research question and objectives	To investigate risk factors for interstitial lung disease (ILD) in patients with epidermal growth factor (EGFR) receptor mutation-positive inoperable or recurrent non-small cell lung cancer (NSCLC) under post-marketing actual status of use of VIZIMPRO
Countory of study	Japan
Author	PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
CR	Complete Response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EGFR	epidermal growth factor receptor
ErbB	HER receptor
HER	human epidermal growth factor receptor
NSCLC	non-small cell lung cancer
PD	Progressive Disease
PR	Partial Response
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SD	Stable Disease

3. RESPONSIBLE PARTIES

The Japan Good Post marketing Study Practice officer

4. AMENDMENTS AND UPDATES

Amendment number	Date	Revision type (substantially or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
Amended 5	18 July 2024	substantially	5.	Changed Milestones	Due to change the scheduled period
			8.2.4.	Changed Planned study period	Due to change the scheduled period
		administrative	STUDY INFORMATIO N	Added Contry of study	Due to the revision of internal format
			4.	Added items of the type of revision	Due to the revision of internal format
			9.2.	Chenged Patient consent	Due to the revision of internal format
			10.2.	Changed Reporting period	Due to the revision of internal format
			12.	Chanded NAME, AND ADDRESS OF CONTRACTOR AS WELL AS SCOPE OF WORK CONTRACTED	Due to the change of consignment of EDC account management work
Amended 4	15 December 2022	administrative	STUDY INFORMATIO N	Department name of the author changed	Organizational change
			5., 8.2.2., 8.2.3., 8.6.1., 8.7., 8.9., 9.4.	Items added and descriptions updated	Editing of descriptions
			6.	Ministerial ordinances and notices updated	Partial revision of ministerial ordinances
			10., 10.4.1.	Japanese translation changed and descriptions edited	Change due to the revision of internal format
			Previous, 12.	Deleted (subsequent section numbers	Editiing of descriptions due to notification of

				moved up)	"Formulation and Publication of Risk Management Plan" dated 18 March 2022
			12.	Scope of work updated and descriptions edited	Expansion of the scope of the contract
			16.1	Name of the department for inquiries changed and descriptions edited	Organizational change
			16.2.	Contact phone number for inquiries changed and desctiptions edited	Change of the contact phone number for inquiries
Amended 3	8 October 2021	substantially	5.	The date of end of data collection and final study report changed	Change due to the extension of the planned study period
			8.2.2.	Study sites changed	Changed in light of the current situation
			8.2.3.	The investigation period and registration period extended	Due to ensure the target number of cases
			8.6.4	The registration period has been extended	Due to prevent registration failures
		administrative	15.	Updated descriptions due to extension of registration period and investigation period	Due to extension of registration period and investigation period
			17.2	E-mail address and etc. changed	Change of E-mail address etc. of Medidatta
Amended 2	7 June 2019	administrative	8.6.1. Case report forms (CRFs)/ Electronic data record 9.1. Patient information	Adjustment of description	Due to a change associated with the revision of the in-house form

			10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS		
			17.2. Contact information for inquiries about the EDC system	Change of e-mail address	Due to a change of e-mail address
Amended 1	11 March 2019	administrative	8.7. Data analysis 13. ADDITIONAL MEASURES THAT MAY BE IMPLEMENTED BASED ON THE STUDY RESULTS AND CRITERIA FOR DETERMINATION OF THE INITIATION 15. OTHER ASPECTS	Adjustment of description	To respond to inquiries
First edition	29 January 2019	NA	N/A	N/A	N/A

5. MILESTONES

Milestone	Planned date
Start of data collection	July 2019
Start of data collection (date of registration of the first patient registered)	24 January 2020
End of data collection	March 2026
End of data collection (date of release of the database)	August 2026
Final study report	December 2026

6. RATIONALE AND BACKGROUND

VIZIMPRO Tablets (dacomitinib hydrate) (hereinafter, this drug) block abnormal signals and inhibit tumor cell proliferation by irreversibly inhibiting the tyrosine kinase activity of epidermal growth factor receptor (EGFR) and mutated EGFR (e.g., deletion of exon 19, point mutation of L858R in exon 21) and other receptors of the ErbB receptor family, HER2 (ErbB2) and HER4 (ErbB4), and by irreversibly inhibiting the activity of homo and heterodimer formed by the ErbB receptor family [EGFR, HER2, ErbB3 (HER3), and HER4]. The marketing authorization of this drug was obtained in January 2019 in Japan as an indication of "EGFR mutation-positive inoperable or recurrent non-small cell lung cancer (NSCLC)".

This study shall be conducted in strict compliance with the "Ministry of Health, Labour, and Welfare (MHLW) Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171, dated December 20, 2004), the "Enforcement of the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (PFSB Notification No. 1220008, dated December 20, 2004), "MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices and Regenerative Medicine Products" (MHLW Ordinance No. 135, dated September 22, 2004), the "Enforcement of the MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices and Regenerative Medicine Products" (PFSB Notification No. 0812-4, dated August 12, 2014), "MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 116, dated October 26, 2017), and "Announcement of the MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products (Regarding the MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products) (PSEHB Notification No. 1026-1, dated October 26, 2017).

7. RESEARCH QUESTION AND OBJECTIVES

This study investigates the following in patients with EGFR mutation-positive inoperable or recurrent NSCLC under post-marketing actual status of use of this drug because interstitial lung disease (ILD) was observed in clinical studies of this drug and the incidence was high in Japanese patients, and ILD has also been observed with other EGFR tyrosine kinase inhibitors and it is considered as an adverse event requiring special attention.

Risk factors for ILD

7.1. Safety specifications

ILD

8. RESEARCH METHODS

8.1. Study design

This study is a multicenter cohort study of patients treated with this drug. The investigators complete the CRF based on the information required by the study that are extracted from medical records such as medical charts created in daily medical practice.

8.2. Setting

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

8.2.1. Registration criteria

This study will be conducted in patients with EGFR mutation-positive inoperable or recurrent NSCLC who have not received this drug.

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

[Indication] *EGFR* mutation-positive inoperable or recurrent NSCLC
[Dosage and administration] The usual adult dosage for oral use is 45 mg of dacomitinib once daily.
The dose should be reduced appropriately according to the patient's condition.

8.2.2. Exclusion criteria

Not specified in this study.

8.2.3. Study sites

The study will be conducted at approximately 300 sites mainly at the department of respiratory medicine, the department of oncology, etc.

8.2.4. Planned study period

The planned period covered by this study is as follows.

Investigation period: July 2019 to March 2026

Registration period: July 2019 to March 2025*

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

8.2.5. Study method

This study will be conducted with the central registration system, and patients who meet the conditions of this study will be registered until data are collected on a target number of patients.

8.2.6. Observation period

The observation period will be 52 weeks from the first day of administration of this drug. However, the observation period will be until the date of treatment discontinuation for patients who discontinue treatment with this drug (adverse events will be reported until 28 days after the date of treatment discontinuation).
In this study, the following booklet type CRF separated by the observation period will be used.

Booklet 01: From the start of administration to Week 24
Booklet 02: From Week 25 to Week 52

8.2.7. Rationale for sample size

In NSCLC patients treated with single-agent dacomitinib at the starting dose of 45 mg QD, the number of days (maximum) from the first day of administration of this drug to the onset date of ILD was 111 days and 238 days in the Japanese population and the overall population, respectively, and the incidence by 90 days and the initial incidence of all grades of ILD were consistently low. In the investigation of risk factors for ILD, which is the objective of this study, it is necessary to accumulate many patients who developed ILD. Since the onset of ILD has been observed within 52 weeks, the observation period of this study was set at 52 weeks.

8.3. Variables

The following information obtained during the observation period of this study will be the variables.

Table 1. Variables and schedule of observation

Variable	At registration	At the start of administration	From the first day of administration to Week 24	Week 25 to Week 52
ID number	●	○		
Gender	●	○		
Birth year	●	○		
Indication	●			
Not applicable to contraindicated cases	●			
First day of administration of this drug	●	○		
Height/body weight		●		
Date of initial diagnosis of the target disease (NSCLC)		●		
EGFR mutation test results		●		
Tumor status		●		
General condition (ECOG PS)		●		
Other patient characteristics (smoking history, occupational and environmental exposure to asbestos, pneumoconiosis, etc., and oxygen administration for treatment of respiratory disease)		●		
Disease history		●		
History of previous drug therapy for NSCLC		●		
Number of prior therapies for NSCLC		●		
History of EGFR-TKI treatment		●		
Pregnancy		●	●	●
Record of use of this drug		●	●	●
Surgical history*		●	●	●
Prior radiotherapy*		●	●	●
Investigation related to ILD*		●	●	●
Tests related to ILD*		●	●	●
Effectiveness evaluation (RECIST)			●	●
Record of continuation/discontinuation of the study			●	●
Confirmation of survival status			●	●
Adverse events			●	●

●, Data entry items; ○, data reflection items; *, including information before the start of administration

8.3.1. Patient characteristics

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

1. ID number
2. Gender
3. Birth year
4. First day of administration of this drug
5. Height/body weight
6. Date of initial diagnosis of the target disease (NSCLC)
7. EGFR mutation test results (date of diagnosis of test results, test methods, and test results)
8. Tumor status (TNM classification and histopathological diagnosis of the target disease)
9. General condition (ECOG PS)
10. Other patient characteristics (smoking history, occupational and environmental exposure to asbestos, pneumoconiosis, etc., and oxygen administration for treatment of respiratory disease)
11. Disease history [name of disease or syndrome (Diagnosis), and classification of past or present illness]
12. History of previous drug therapy for NSCLC
13. Number of prior therapies for NSCLC
14. History of EGFR-TKI treatment
15. Pregnancy status [Female only]*

* Information from the first day of administration of this drug to the end date of the observation period should be entered.

8.3.2. Administration record of targeted drug

The following information will be recorded regarding the status of use of this drug until the end of the observation period (or date of discontinuation).

1. Daily dose
2. Period of administration
3. Reason for change/interruption

8.3.3. History of surgery for NSCLC

The following information on the history of surgery performed from baseline to the end of the observation period (or date of discontinuation) should be recorded.

1. Site

2. Date of surgery

8.3.4. Prior radiotherapy for NSCLC

The following information on the history of radiotherapy performed from baseline to the end of the observation period (or date of discontinuation) should be recorded.

1. Site

2. Treatment period

8.3.5. Investigation related to ILD

If ILD occurs, the following information will be recorded for investigations related to ILD conducted from baseline to the end of the observation period (or 28 days after discontinuation).

1. Symptoms related to ILD

2. Drug therapy for ILD (drug name, route of administration, and effect)

3. Non-drug therapy for ILD (name and effect of non-drug therapy)

8.3.6. Tests related to ILD

If ILD occurs, the following information will be recorded for tests related to ILD performed from baseline to the end of the observation period (or 28 days after discontinuation). Also, the sponsor will request the investigator to provide the results of chest X-ray and chest CT (image photographs or data), and the investigator will provide them to the sponsor.

1. Laboratory tests related to ILD [PaO2, A-aDO2, β-D-glucan, cytomegalovirus test, urinary Legionella antigen, KL-6, SP-D, SP-A, CRP, bronchoalveolar lavage lymphocyte (%), and bronchoalveolar lavage neutrophil (%)]

2. Lung biopsy (test date, test method, site, and findings)

3. Bacterial culture test (test date, sample, and findings)

4. Diagnostic imaging [chest X-ray and chest CT] (name of test item, test date, and findings)

8.3.7. Evaluation related to ILD

If ILD is observed between the first day of administration of this drug and the end date of the observation period (or 28 days after discontinuation), the investigator will evaluate ILD. Thereafter, an external medical specialist will separately evaluate ILD. The details of evaluation by the external medical specialist will be described in the written procedures for evaluation related to ILD.

8.3.8. Record of continuation/discontinuation of the study

If administration of this drug could not be continued at the end of the observation period (or date of discontinuation), the primary reason for discontinuation should be selected from the following options and recorded.

1. Continuation/discontinuation

2. Last observation day

3. Reason for discontinuation

Insufficient clinical effectiveness

Adverse events

Patient's death

No revisit

Transferred to other hospital/department

Others (If "Others," enter the reason.)

8.3.9. Confirmation of survival status

Survival status will be checked at the end of the observation period (or date of discontinuation). If death is confirmed, the primary reason for death should be selected from the following options and entered.

[Cause of death]

Progression of NSCLC

ILD

Others

Unknown

8.3.10. Effectiveness evaluation

The effectiveness of this drug will be evaluated for the effectiveness evaluation variables in "Response Evaluation Criteria in Solid Tumors Guidelines - Revised Version 1.1 -" for each separate booklet of the CRFs, and the results will be recorded. If administration of this drug is discontinued, the evaluation before discontinuation of this drug should be recorded.

Assessment of tumor response: Tumor response will be assessed according to RECIST criteria. In the classification of tumor lesions at the start of administration of this drug, target lesions and non-target lesions will be identified, and in addition to the results of assessment of tumor response in each tumor lesion during the observation period, presence or absence of new lesions will be confirmed to evaluate overall response.

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

2. Evaluation after the start of administration of this drug

Presence or absence of effectiveness evaluation

Date of best overall response assessment

Best overall response (CR, PR, SD, PD, not evaluable)

8.3.11. Adverse events

An adverse event is any untoward medical occurrence in a patient administered a medicinal product. Occurrence of ILD from the first day of administration of this drug to the end date of observation period (or 28 days after discontinuation) should be confirmed and the following information should be recorded. If ILD is observed, the investigator will take appropriate measures, promptly notify the sponsor, and if the causal relationship with this drug cannot be ruled out, confirm the course until the ILD or its sequela disappears or becomes stable to an extent acceptable by the investigator and the sponsor.

1. Presence/absence of onset of ILD

2. Name of adverse event

3. Date of occurrence

4. CTCAE v4.0 Grade

5. Treatment (changes in administration of this drug, and additional treatment for adverse events)

6. Seriousness

7. Outcome, date of confirmation of outcome, date of resolution/date of recovery/date of death

8. Causal relationship to this drug, factors other than this drug related to the onset of adverse events

8.4. Data sources

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

8.5. Study size

8.5.1. Planned sample size

799 patients with EGFR mutation-positive inoperable or recurrent NSCLC (safety analysis set)

8.5.2. Rationale for sample size

In Japanese NSCLC patients treated with single-agent dacomitinib at the starting dose of 45 mg QD, the incidence of all-causality ILD was 5.9% (6/101 patients). In order to evaluate the effect of risk factors for ILD under the actual status of use of this drug, the sample size was set so that a statistically significant relative risk can be detected between subgroups with and without risk factors. Assuming that the incidence of ILD in the low-risk and high-risk populations is 5.9% and 11.8%, respectively (equivalent to 2.0 relative risks), and that the ratio of the number of subjects in the low-risk and high-risk populations is 1: 3, the number of patients in whom risk factors can be detected under a significance level (two-sided) of 15% and a power of 80% is 799. Assuming that 10% of the enrolled patients will be excluded from the safety analysis set for some reason, the number of enrolled patients was set at 888.

8.6. Data management

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

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

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

8.6.2. Record retention

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

8.6.3. Data collection method (EDC)

The data for this study will be entered in the CRFs and confirmed by using the electronic system on the internet designed for collecting post-marketing survey data [Electronic Data Capture (EDC); hereinafter, this system] provided by the sponsor.

8.6.4. Patient registration (EDC)

The investigator will enter the registration items on the patient registration screen of this system. Patient registration will be performed within 84 days including the first day of administration of this drug.

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

8.6.5.1. Data entry

The investigator should confirm the survey items, and enter the data into this system based on source documents such as medical charts.

8.6.5.2. Data revision

Upon receiving query from the sponsor on the contents of the CRF (follow-up survey), the investigator will again confirm the contents of source documents such as medical charts, and as required, correct relevant sections.

8.6.5.3. Submission

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

8.7. Data analysis

1. Analysis sets

The safety analysis set (SAS) consists of a full analysis set (FAS) that is as closer as possible to all patients who received this drug. The effectiveness analysis set consists of the SAS excluding patients such as those with non-target diseases for whom no effectiveness evaluation has been reported at all. Detailed definitions will be provided in the statistical analysis plan (SAP).

2. Method of analysis

- Safety analysis

The number and proportion of patients with ILD will be tabulated by subgroup by risk factor. ILD based on the evaluation by an external medical specialist (See 8.3.7.) will be analyzed separately. In addition, the number and proportion of patients with adverse reactions will be tabulated. The details of other analysis plans will be described in the SAP.

- Effectiveness analysis

The efficacy rate will be calculated. The efficacy rate is defined as the proportion of patients with a best overall response of CR or PR in the effectiveness analysis set. Further details of the analysis plan will be provided in the SAP.

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.

8.8. Quality control

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

8.9. Limitations of the research methods

There may be potential limitations in this study:

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

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

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

8.10. Other aspects

Not applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

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

Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

9.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, or it is an information provision based on the law (even though that involve data subject to privacy laws according to applicable legal requirements), obtaining informed consent from patients by Pfizer is not required. 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. 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 or used for other research on pharmaceuticals, medical care, public health, etc. other than 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, or to use for other research 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 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 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 "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. Recording and reporting requirements

The following table summarizes the requirements for recording safety events in the CRFs and for reporting safety events to Pfizer Safety on the Non-Interventional Study Adverse Event Report Form (NIS AE Report Form). These requirements are described for three types of events: (1) serious adverse events (See Table), (2) non-serious adverse events (See Table), and (3) scenarios related to drug exposure including exposure during pregnancy, exposure during breast feeding, medication error, drug overdose, drug misuse, extravasation, lack of effectiveness, and occupational exposure (not applicable in this study). These events are defined in the "Definitions of safety events" section.

Safety events	Record in the CRF	Report the event to Pfizer Safety within 24 hours of awareness using the NIS AE Report Form
Serious adverse events	ILD	ILD
Non-serious adverse events	ILD	Absence
Scenarios involving exposure to this drug, including exposure during pregnancy, exposure during breastfeeding, medication error, drug overdose, drug misuse, extravasation, lack of efficacy, and occupational exposure	Absence	Absence

For each adverse event, the investigator must obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (See "Serious adverse events" section below).

Safety events that are reportable to the safety department in the table above must be reported to Pfizer within 24 hours of the investigator's knowledge of the event, **whether or not the investigator believes that the event is related to VIZIMPRO Tablets**. In particular, if the serious adverse event is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available information. This timeframe also applies to additional new (follow-up) information received on a previously reported safety event report. In the rare event that the investigator does not become aware of the occurrence of a

safety event immediately, the investigator is to 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 identified in the far right column of the table above that require reporting to Pfizer within 24 hours of awareness, the investigator must perform a follow-up and report any additional information to Pfizer in accordance with the 24 hour timeframe. In addition, the investigator may be requested by Pfizer to obtain specific additional information in an expedited manner. This information is more detailed than the information recorded in the CRF. In general, this information will include sufficient detail to complete the medical assessment of the adverse event and to allow for independent causality assessment. Information on the event (e.g., concomitant drugs, complications) must also be provided. In the event of a patient death, a summary of available autopsy findings must be promptly provided to Pfizer or its designated representative.

10.2. Reporting period

The reporting period of safety events (see table above) for each patient in the CRF to the safety department will start at the time of the first administration of VIZIMPRO Tablets to the patient and end at the end of the observation period of the study, but will last until at least 28 days (calendar day) after the last administration of this drug. If safety events of the types listed in the table above occur during this reporting period, the investigator will submit a report to Pfizer Safety (or persons to whom Pfizer outsources such operations). If a patient receives this drug on the last day of the observation period, the reporting period will be extended by 28 days (calendar day) after the end of the observation period.

If the investigator learns of any serious adverse event occurring at any time after completion of the study and he/she considers the serious adverse event to be related to VIZIMPRO Tablets, the serious adverse event will also be reported to Pfizer Safety.

10.3. Causality assessment

The investigator will be asked to assess and record causality. In addition, the investigator should obtain sufficient information to determine the causal relationship of each adverse event. The investigator will be required to follow up on adverse events related to VIZIMPRO Tablets until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

The investigator's assessment of causality will be based on whether there is a reasonable possibility that VIZIMPRO Tablets caused or contributed to the adverse event. If the investigator's final determination of causality is "unknown" and he/she is unable to determine whether VIZIMPRO Tablets caused the event, the safety event must be reported within 24 hours.

If the investigator is unable to determine the cause of the event, but he/she determines that VIZIMPRO Tablet did not cause the event, this should be clearly documented on the CRF and NIS AE Report Form.

10.4. Definitions of safety events

10.4.1. Adverse events

An adverse event 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 adverse events include, but are not limited to:

- Abnormal test findings (see below for conditions under which abnormal laboratory findings constitute an adverse event.)
- Clinically significant symptoms and signs
- Changes in physical examination findings
- Hypersensitivity
- Lack of effectiveness
- Drug abuse
- Drug dependence

In addition, signs and symptoms that occur due to the following causes may be included:

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

<u>Abnormal test findings</u>

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

- Associated with symptoms related to test results
- Additional diagnostic testing or medical/surgical intervention indicated
- Test result leads to a change in dosing or discontinuation of the study, or addition of concomitant drug treatment or other treatment.
- The investigator or Pfizer judges it to be an adverse event.

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

10.4.2. Serious adverse events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric preparations) at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not qualify as an adverse event)
- Results in persistent or significant disability/incapacity (a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal within the safety reporting period. Hospitalization for signs and symptoms of disease progression should not be reported as a serious adverse event. However, if the malignancy during the study or within the safety reporting period has a fatal outcome, the event leading to death must be recorded as an adverse event and reported as a Grade 5 serious adverse event.

Medical and scientific judgment should be exercised in deciding whether an event is an important medical event. Important medical events may not be immediately life-threatening or result in death or hospitalization. However, if the event jeopardizes the patient or requires intervention to prevent one of the outcomes listed above, it should be reported as a serious adverse event.

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.

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 are considered unexpected and will be handled as serious expedited cases by the safety department. 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 of an existing admission. Hospitalization also includes transfer within the hospital to another department or an acute/intensive care unit (transfer from the psychiatric ward to the medical ward, from the medical ward to the coronary care unit, from the neurological ward to the tuberculosis ward, etc.). Emergency room visits are not necessarily hospitalizations; however, events leading to emergency room visits should be evaluated for medical significance.

Hospitalization without a medical adverse event is not in itself an adverse event and is not reportable. For example, the following hospitalization without medical adverse events does not need to be reported:

- Social admission (e.g., no patient/subject accommodation)
- Administrative admission (e.g., for annual medical checkup)
- Optional admission not associated with a precipitating clinical deterioration (e.g., optional cosmetic surgery)
- Admission for observation without a medical adverse event
- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with worsening of the preexisting condition (e.g., close examination for laboratory abnormalities present before the start of treatment)
- Admission during the study period specified in the protocol (e.g., tests and procedures specified in the protocol)

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

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

Company name: EPS Corporation
Address: 2-23 Shimomiyabicho, Shinjuku-ku, Tokyo
Scope of work contracted: Works related to this study other than administrative works, including registration, establishment of the post-marketing surveillance data collection system (EDC), data management, and tabulation and analysis.

Company name: Medidata Solutions
Address: 2-7-2 Marunouchi, Chiyoda-ku, Tokyo
Scope of work contracted: Establishment, operation and maintenance of the post-marketing surveillance data collection system (EDC), etc.

Company name: A2Helthcear
Address: 1-4-1 Koishikawa, Bunkyo-ku, Tokyo
Scope of work contracted: Account management work of the post-marketing surveillance data collection system (EDC), etc.

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

Review the RMP including the following contents at the scheduled timing of milestones.

- Review the necessity for changing the contents of risk minimization activities for the safety specifications (ILD) of this study.

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

Time of the periodic safety update report: To periodically check the status of occurrence of events related to safety specifications in this study and comprehensively examine and report safety.

Timing of completion of the study and at the time of application for reexamination: For the final examination and reporting of safety concerning the results of this study.

15. 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 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 protocol will be amended when the partial change in the dosage and administration or indication is approved during the reexamination period (except when the reexamination period is newly designated), etc.

2. Actions to be taken for any problem or issue

Revision of the package insert and conduct of a new post-marketing surveillance or new post-marketing clinical trials should be considered for the following cases: a significant increase in the frequency of adverse reactions; any effectiveness or safety concern compared to pre-approval is suggested.

16. CONTACT INFORMATION

16.1. Contact information for inquiries about the study

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

16.2. Contact information for inquiries about the EDC system

Name	Medidata Helpdesk
Business Hours	Weekdays: 9:00-20:00 (excluding Saturdays, Sundays, and holidays, year end and beginning)
TEL	PPD (Pfizer dedicate line)
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

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable