(Appendix)

Vyndaqel Capsules Special Investigation

- Investigation on patients with transthyretin amyloid cardiomyopathy -

Full Protocol

Pfizer Japan Inc.

STUDY INFORMATION

Title	Vyndaqel Capsules Special Investigation -Investigation on patients with transthyretin amyloid cardiomyopathy-
Protocol number	B3461064
Protocol version identifier	8
Date	24 October 2023
Active substance	Tafamidis meglumine, Tafamidis
Medicinal product	Vyndaqel® Capsules 20 mg, Vynmac® Capsules 61 mg
Research question and objectives	To comprehend information on the long-term safety (e.g., onset status of adverse reactions), etc. of patients who are treated with Vyndaqel Capsules 20 mg (hereinafter referred to as Vyndaqel) for the treatment of transthyretin amyloid cardiomyopathy. When Vynmac Capsules 61 mg (hereinafter referred to as Vynmac) is used, conduct the study to grasp information on safety (e.g., onset status of adverse reactions), etc. during the observation period. [Conditions for approval for Vyndaqel] Because the number of study participants in Japan is very limited, the background information of patients using this drug* should be grasped by conducting a use-result survey in all patients while the data on a certain number of patients is accumulated after marketing and data on the safety and effectiveness of this drug should be collected early to take measures necessary for proper use of this drug. *: Vyndaqel [Conditions for approval for Vynmac] Because the number of study participants in Japan is very limited, the background information of patients using this drug** or Vyndaqel Capsules 20 mg should be grasped by conducting a use-result survey in all patients while the data on

	a certain number of patients is accumulated after marketing and data on the safety and effectiveness of this drug or Vyndaqel Capsules 20 mg should be collected early to take measures necessary for proper use of this drug. **: Vynmac
Author	PPD PPD

1. TABLE OF CONTENTS

1. TABLE OF CONTENTS 4
2. LIST OF ABBREVIATIONS 7
3. RESPONSIBLE PARTIES 8
4. AMENDMENTS AND UPDATES 8
5. MILESTONES 9
6. RATIONALE AND BACKGROUND 9
7. RESEARCH QUESTION AND OBJECTIVES 10
7.1. Safety specifications 11
8. RESEARCH METHODS 11
8.1. Study design 11
8.2. Setting 11
8.2.1. Registration criteria 11
8.2.2. Exclusion criteria 12
8.2.3. Study sites 12
8.2.4. Planned study period 12
8.2.5. Study procedures 12
8.2.5.1. Study method 12
8.2.6. Observation period 13
8.3. Variables 15
8.3.1. Patient characteristics 16
8.3.2. Administration record of targeted drugs 17
8.3.3. Concomitant therapy 18
8.3.3.1. Drug therapy 18
8.3.3.2. Non-drug therapy (device therapy) 18
8.3.4. Tests/clinical laboratory tests 18
8.3.4.1. Clinical laboratory tests 18
8.3.4.2. Clinical symptoms 19
8.3.5. Presence or absence of pregnancy during the observation period (only for female patients) 19
8.3.6. Implementation status of the study and records at discontinuation 19
8.3.7. Confirmation of survival 20
8.3.8. Adverse events 20
8.4. Data sources 21

8.5. Study size 21
8.5.1. Sample size 21
8.5.2. Rationale 21
8.6. Data management 21
8.6.1. Case report forms (CRFs)/Electronic data record 21
8.6.2. Record retention 22
8.6.3. Data collection method (EDC) 22
8.6.4. Patient registration (EDC) 22
8.6.5. Points to consider for completion, revision, and submission of CRF (EDC) 22
8.6.5.1. Data entry 22
8.6.5.2. Data revision 23
8.6.5.3. Submission 23
8.6.6. Data collection method (paper CRFs) 23
8.6.7. Patient registration (paper CRFs) 23
8.6.8. Points to consider for completion, revision, and submission of CRF (paper CRFs) 23
8.6.8.1. Data entry 23
8.6.8.2. Data revision 23
8.6.8.3. Submission 23
8.6.9. All cases survey registration 24
8.7. Data analysis 24
8.8. Quality control 25
8.9. Limitations of the research methods 25
8.10. Other aspects 25
9. PROTECTION OF HUMAN SUBJECTS 25
9.1. Patient information 25
9.2. Patient consent 26
9.3. Institutional Review Board (IRB)/Ethics Committee (EC) 27
9.4. Ethical conduct of the study 27
10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 27
10.1. Requirements 27
10.2. Reporting period 28
10.3. Causality assessment 29
10.4. Definitions of safety events 29
10.4.1. Adverse events 29

10.4.2. Serious adverse events 30
10.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours 32
11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 35
12. NAME, AND ADDRESS OF CONTRACTOR AS WELL AS SCOPE OF WORK CONTRACTED 36
13. ADDITIONAL MEASURES THAT MAY BE IMPLEMENTED BASED ON THE STUDY RESULTS AND CRITERIA FOR DETERMINATION OF THE INITIATION 36
14. SCHEDULED TIMING OF MILESTONES FOR EVALUATING IMPLEMENTATION STATUS AND OBTAINED RESULTS OR REPORTING TO THE PMDA, AND THEIR RATIONALES 36
15. OTHER NECESSARY MATTERS 37
16. CONTACT INFORMATION 37
16.1. Contact information for inquiries about the study 37
16.2. Contact information for inquiries about the EDC system (For the study using the EDC) 37
17. REFERENCES 37
18. LIST OF TABLES 38
19. LIST OF FIGURES 38
ANNEX 1. LIST OF STAND ALONE DOCUMENTS 38
ANNEX 2. ADDITIONAL INFORMATION 38

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ATTR-CM	transthyretin amyloid cardiomyopathy
BNP	brain natriuretic peptide
EDC	electronic data capture
N/A	not applicable
NT-pro BNP	N-terminal prophormone brain natriuretic peptide
SAP	statistical analysis plan
TTR	transthyretin
TTR-FAP	transthyretin-type familial amyloid polyneuropathy

3. RESPONSIBLE PARTIES

The Japan Good Post-marketing Study Practice officer

4. AMENDMENTS AND UPDATES

Amendment number	Date	Type of amendment (substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
Amended 7	24 October 2023	Substantial	4, 6, 8.2.4, 8.2.5, 8.2.6, 8.3, 8.3.1, 8.6.4, 8.6.7, 8.6.9, 9.3, 12	Deletion of the descriptions regarding registration not requiring preparation of case report forms.	Because registration not requiring preparation of case report forms was completed based on Q&A 5 in the Administrative Notice dated 10 August 2023, and the text was reviewed and corrected.
Amended 6	17 November 2022	Administrative	5, 6, 8.2.2, 8.2.5.1, 8.3, 8.6.5.2, 8.6.9, 8.7, 8.9, 9, 9.4, 10.1, 10.4.1, 10.4.2, 10.4.3, 12, 16	Change of the contact information, Change of the reference to the organizational structure, Minor corrections.	Because the text was reviewed and corrected in association with the change of the contact information and the change of the reference to the organizational structure.
Amended 5	12 January 2022	Administrative	STUDY INFORMATION, 13,17.1	Change of the Department Name , Change of the scope of work contracted.	Because of organization changes, and because of scope of work contracted was updated.
Amended 4	18 October 2021	Substantial	6, 7, 7.1, 8.1, 8.2.1, 8.2.5.1, 8.3, 8.3.1, 8.3.2, 8.3.6, 8.3.8, 8.5, 8.6.6, 8.6.9, 8.7, 10.1, 10.2, 10.3, 10.4.3, 13, 14, 15, 17.2, 19, 20	Add that information on Vynmac treatment will be also collected to evaluate safety. Minor corrections.	Because the study will be continued when Vynmac is used to collect information on Vynmac treatment during the observation period, and because the text was reviewed and corrected.
Amended 3	24 March 2021	Substantial	8.2.4, 8.2.5.1, 8.2.6, 8.3, 8.3.1, 8.6.4, 8.6.7, 8.6.9	Change of the registration period in association with shifting to patient registration only. Add patients to be registered,	Because of shifting to patient registration only

				registration method, etc.	
Amended 2	05 July 2019	Administrative	8.6.1	Add the data correction method	Because the data correcting method was added.
			10	Add sections	Because the Safety Reporting Language provided as attachment was merged.
Amended 1	25 April 2019	Administrative	8.2.4	Change of the registration period	Because the timing to start the registration period was adjusted to the timing to start this study
Final	29 March 2019	N/A	N/A	N/A	N/A

5. MILESTONES

Milestone	Planned date
Start of data collection (start date of observation for the first subject)	March 2019
Start of data collection (date of registration of the first subject)	03 October 2019
End of data collection (end date of observation for the last subject)	September 2023
End of data collection (date of release of the database)	November 2024
Final study report	April 2025

6. RATIONALE AND BACKGROUND

Vyndaqel obtained the marketing authorization for the indication of "suppression of progression of peripheral neuropathy in transthyretin-type familial amyloid polyneuropathy" in September 2013. After an additional application for the indication of "transthyretin amyloid cardiomyopathy (hereinafter referred to as ATTR-CM)" was filed in November 2018, the approval for the additional application was obtained in March 2019.

Vyndaqel is an orally available low molecular weight compound that binds to the thyroxine binding site of TTR and specifically stabilizes the TTR tetramers in plasma for both genetic variants and wild-type. This mechanism of action is expected to inhibit dissociation of the tetramers into monomers, which is a rate-limiting step in amyloid formation, suppress amyloid deposition in tissues such as the myocardium, and delay or deter the progression of ATTR-CM disease.

"Vyndaqel Capsules Special Investigation - Investigation on patients with transthyretin amyloid cardiomyopathy -" (hereinafter referred to as this study) will be conducted to

comprehend information on the safety (e.g., onset status of adverse reactions), etc. of patients who are treated with Vyndaqel for the treatment of ATTR-CM.

Vynmac was approved for marketing in September 2021 for ATTR-CM because it demonstrated the same safety and tolerability as those of tafamidis meglumine 80 mg (20 mg x 4 capsules) containing the same physiologically active ingredient in patients with ATTR-CM. In this study, Vynmac is also investigated: when Vynmac is used during the observation period, observation will be also continued until the planned observation period is completed to comprehend information on the safety (e.g., onset status of adverse reactions), etc. of Vynmac.

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 the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, Medical Devices, and Regenerative Medical Products" (MHLW Ordinance No. 135, dated September 22, 2004), the "Enforcement of the MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, 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 the "Announcement of the MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (Regarding the MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products) (PSEHB Notification No. 1026-1, dated October 26, 2017).

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this study is to comprehend information on the long-term safety (e.g., onset status of adverse reactions), etc. of patients who are treated with Vyndaqel for the treatment of ATTR-CM after the approval for the indication of this drug for ATTR-CM was obtained. When Vynmac is used, the study will be also conducted to grasp information on safety (e.g., onset status of adverse reactions), etc. during the observation period.

[Conditions for approval for Vyndaqel]
Because the number of study participants in Japan is very limited, the background information of patients using this drug* should be grasped by conducting a use-result survey in all patients while the data on a certain number of patients is accumulated after marketing and data on the safety and effectiveness of this drug should be collected early to take measures necessary for proper use of this drug.

*: Vyndaqel

[Conditions for approval for Vynmac]
Because the number of study participants in Japan is very limited, the background information of patients using this drug** or Vyndaqel Capsules 20 mg should be grasped by conducting a use-result survey in all patients while the data on a certain number of patients is accumulated after marketing and data on the safety and effectiveness of this drug or Vyndaqel Capsules 20 mg should be collected early to take measures necessary for proper use of this drug.

**: Vynmac

7.1. Safety specifications

Important Potential Risks: Hepatotoxicity, hypersensitivity reactions, reproductive and developmental toxicity, infection, incorrect product selection between Vyndaqel and Vynmac

Important Missing Information: Safety in patients with severe hepatic impairment, administration to patients with variants

8. RESEARCH METHODS

8.1. Study design

This study is a multi-center cohort study of patients with ATTR-CM receiving Vyndaqel or Vynmac (hereinafter collectively referred to as this drug). The investigators complete the collection of case report forms (CRFs) based on the information extracted from the medical records created in daily medical practice.

8.2. Setting

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

8.2.1. Registration criteria

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

- The purpose of treatment with this drug is ATTR-CM.

  *Patients who have participated in clinical studies of ATTR-CM and continue to receive treatment of ATTR-CM are eligible for inclusion.

Refer to the latest package insert of this drug for "indications" and "dosage and administration" when this drug is administered. The descriptions on ATTR-CM are excerpted and shown below:

[Indication]
Transthyretin amyloid cardiomyopathy (wild-type and variants-type)

[Dosage and administration]
Transthyretin amyloid cardiomyopathy

<Vyndaqel Capsules 20 mg>
The usual adult dose is 80 mg of tafamidis meglumine orally once daily. The dose may be decreased if not tolerated.

<Vynmac Capsules 61 mg>
The usual adult dose is 61 mg of tafamidis orally once daily.

8.2.2. Exclusion criteria

No exclusion criteria are set for this study.

8.2.3. Study sites

This study will be conducted at approximately 150 sites including the Departments of Cardiology, Department of Neurology, and Department of Internal Medicine, etc.

8.2.4. Planned study period

The planned period covered by this study is as follows.

Investigation period: March 2019 to September 2023 (From the start date of observation for the first subject to the end date of observation period for the last subject)

Registration period: March 2019 to March 2021 (From the start date of administration for the first subject to the start date of administration for the last subject)

However, CRFs may be collected when additional information needs to be collected.

8.2.5. Study procedures

8.2.5.1. Study method

All patients surveillance system: This study will be conducted with all patients surveillance system that all patients will be registered until data are collected on a target number of patients.

This study investigates patients who used a marketed product of this drug after the approval for the indication for ATTR-CM is obtained at contract sites. This study targets patients who used this drug until contracts are concluded with sites requested to conduct the study and also

includes patients who used this drug after the conclusion of contracts (including retrospective patients).

When additional information needs to be collected, the investigator shall complete a CRF upon request of the Sponsor (Pfizer Japan Inc., hereinafter the same). When a patient, whose CRF is to be collected, is transferred to another hospital during the observation period, the investigator shall inform the Sponsor of the name of the transferred medial institution. The Sponsor shall conclude a contract to conduct this study with the transferred medial institution and conduct the study there.

8.2.6. Observation period

30 months (Week 130) from the start of administration (Day 1)

However, for patients who discontinued this drug during the observation period, the observation period will be until the first visit after the date of discontinuation.

In this study, information will be collected using a booklet type CRF. Information during the following periods will be entered in each booklet.

If the patient is transferred to another hospital or department (hereinafter referred to as hospital transfer) during the observation period, the patient will be newly registered even at the transferred site and the CRF will be completed. If the patient is transferred to another hospital, the patient registration number of the original site will be conveyed to the transferred site. Although the patient will be given a new patient registration number at the transferred site at the time of registration, he or she will be determined to be a transferred patient by reporting the patient registration number of the original site and his/her data will be handled as the same patient. If the time point of 30 months after the start date of initial administration can be identified for the transferred patient, the observation period at the transferred site may be reset so that the total observation period of the patient in this study will become 30 months.

Figure 1. Observation period for each booklet

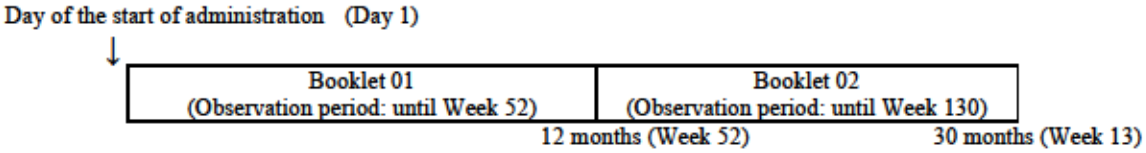
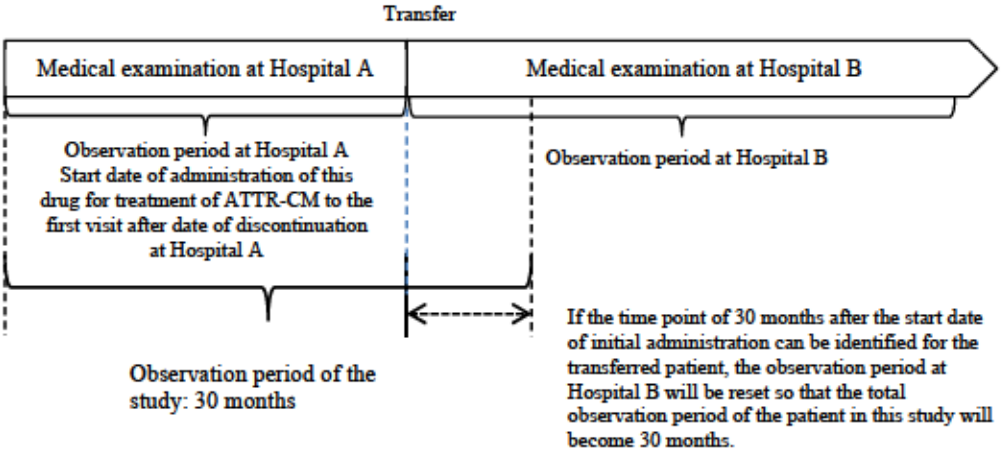


Figure 2. Setting of observation period for transferred patients



8.3. Variables

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

For patients transferred from the clinical trial, the first administration day of a marketed product of this drug will be the first day of administration of this drug.

Table 1. Variables and schedule of activities

Variables	Registration form	Booklet 01		Booklet 02
		At start of administration of this drug	Start of administration to Month 12 (Week 52) of treatment	Week 53 to Month 30 (Week 130) of treatment
ID number	●	*1		
Gender	●	*1		
First day of treatment with this drug for ATTR-CM	●			
Confirmation of eligibility	●			
Identification of transferred patients	●	*1		
Usage experience of this drug	●*2	*1		
Birth year/age	●*3	*1		
Disease type of ATTR-CM	●*3	*1		
Severity of heart failure (NYHA Functional Classification)	●*3	*1	●	●
Inpatient/outpatient status		●*3		
Height/body weight		●*3		
Clinical laboratory test (serum albumin)		●*3		
Target disease		●*3		
Genotype of ATTR-CM (only for patients with variants)		●*3		
Presence/absence of liver/renal impairment, (only for liver impairment) severity		●*3		
Complication		●*3		
Presence/absence of pregnancy during the observation period (only for female patients)			●	●
Implementation status of the study and records at discontinuation			●	●
Confirmation of survival			●	●
Administration record of targeted drug			←→	←→
Concomitant therapy (Drug therapy/Device therapy)			←→	←→
Clinical laboratory tests			←→	←→
Adverse events			←→	←→
Obtaining consent for publication of results		←	→	→

*1 While the contents of the registration form will be automatically reflected, the investigator will check the contents again and make corrections as necessary.

*2 Not collected in the case of transferred patients.
*3 Not collected if the patient is transferred to another hospital and the patient registration number of the original site is entered.

8.3.1. Patient characteristics

1. Enter the information at the start of administration of this drug into the registration form.
    a. Site information (if the study is conducted using paper CRFs)
    b. ID number
    c. Gender
    d. First day of treatment with this drug for ATTR-CM (first administration day of a marketed product of this drug for patients transferred from clinical trials, hereinafter the same)
    e. Identification of transferred patients (in the case of transferred patients, enter the patient registration number of the original site)
    f. Usage experience of this drug [administered this drug for the first time, transferred from clinical trials, or in treatment for transthyretin-type familial amyloid polyneuropathy (TTR-FAP) but also started to receive the treatment of ATTR-CM] (no entry is necessary for transferred patients)

    If the patient is a transferred patient and the patient registration number of the original site has been entered, the entries for the following items g. to i. are not necessary (the entries are necessary even for the transferred patient if the patient registration number of the original site is not clear)

    g. Birth year (known at the start of administration of this drug) (if the birth year cannot be disclosed, enter the age at the start of administration of this drug)
    h. Disease type of ATTR-CM (wild-type, variant, or unknown)
    i. Severity of heart failure (NYHA Functional Classification)
2. The following will be recorded in CRF at the start of administration of this drug. If the contents of the registration form have been reflected, the investigator will check the contents again and make corrections as necessary.
    a. ID number
    b. Gender

c. Identification of transferred patients (in the case of transferred patients, enter the patient registration number of the original site)

d. Usage experience of this drug (administered this drug for the first time, transferred from clinical trials, or in treatment for TTR-FAP but also started to receive the treatment of ATTR-CM) (no entry is necessary for transferred patients)

If the patient is a transferred patient and the patient registration number of the original site has been identified, the entries for the following items e. to o. are not necessary (the entries are necessary even for the transferred patient if the patient registration number is not clear)

e. Birth year/age

f. Inpatient/outpatient status

g. Height (cm)

h. Body weight (kg)

i. Clinical laboratory test (serum albumin)

j. Target disease

k. Disease type of ATTR-CM (wild-type, variant, or unknown)

l. Genotype of ATTR-CM (only for patients with variants)

m. Severity of heart failure (NYHA Functional Classification)

n. Presence/absence of liver impairment/renal impairment*, (only for liver impairment) severity

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

o. Confirmation of complication [enter the names of chronic diseases including TTR-FAP (including allergy), diseases requiring treatment, diseases or disorders with sequelae, diseases that are cured after a certain post-treatment follow-up, and other diseases or syndromes which are considered problematic]

8.3.2. Administration record of targeted drugs

The following information will be recorded for the targeted products.

1. Drug name (Vyndaqel, Vynmac)

2. Daily dose
3. Number of doses per day
4. Treatment Period
5. Reason for change/washout

8.3.3. Concomitant therapy

8.3.3.1. Drug therapy

For all drugs used during observation period, the following information should be recorded.

1. Drug name
2. Route of administration
3. Start date (the date entry is not necessary if the drug has been administered before the start of the study)
4. End date
5. Purpose of administration (for treatment of ATTR-CM, procedure for adverse events, or others)

8.3.3.2. Non-drug therapy (device therapy)

The presence or absence of device therapy during the observation period should be recorded. If the treatment is started during the observation period, the start date should be recorded (the date entry is not necessary if the drug has been administered before the start of the study).

1. Device therapy
2. Start date

8.3.4. Tests/clinical laboratory tests

8.3.4.1. Clinical laboratory tests

The results of tests performed before the start date of administration (including the start date of administration) and during the observation period of each booklet (or until the first visit date after the date of discontinuation of this drug) should be recorded. If the abnormal value is clinically significant compared to the value before dosing, this information should also be recorded in detail in the adverse event field.

1. NT-proBNP
2. BNP

3. Troponin I

4. Troponin T

8.3.4.2. Clinical symptoms

The following clinical symptoms should be recorded at the start of administration, Week 52, Week 130, and at the time of discontinuation.

- NYHA Functional Classification

Table 2. NYHA Functional Classification*

*Excerpted from Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure (2017 Revised Version)

8.3.5. Presence or absence of pregnancy during the observation period (only for female patients)

The presence or absence of pregnancy at the end point of observation period in each booklet (or until the first visit date after the date of discontinuation of this drug) should be recorded. If pregnancy is found during the observation period, the information should be collected separately from the CRF.

8.3.6. Implementation status of the study and records at discontinuation

The administration status of this drug at the end point of observation period in each booklet should be confirmed. If the patient discontinued the administration of this drug by the end point of observation period in each booklet, data at the first visit after the date of discontinuation should be recorded regardless of the reason for discontinuation. If the administration of this drug is continued, it should be entered as completed. If the administration is discontinued, only one of the following primary reasons should be selected. If the primary reason for discontinuation is an adverse event or others (abnormal laboratory test value), necessary information should be recorded in the adverse event field.

1. End date of the observation period (or the date of the first visit after the date of discontinuation)

2. Status at the end point

- Completed
- Insufficient clinical effectiveness
- Recovery or effective
- Adverse events
- Transferred to other hospital/department
- Lost to follow-up
- Others

8.3.7. Confirmation of survival

The survival status until the end date of observation period in each booklet (or until the first visit date after discontinuation of this drug) should be recorded. In the case of death, the date of death and cause of death [cardiovascular event, or others (including unknown)]should be recorded.

8.3.8. Adverse events

Occurrence of adverse events from the start date of administration of this drug to the end date of observation period (or first visit date after the date of discontinuation of this drug) should be confirmed and the following information should be recorded.

Also, further investigation should be separately conducted, if deemed necessary by Sponsor for patients who experienced a serious adverse reaction, an unexpected adverse reaction or other adverse reactions not listed in the package insert.

- Presence/absence of adverse event
- Name of adverse event
- Date of occurrence
- Seriousness
- Change in the administration of this drug
- Intervention
- Outcome

- Causal relationship to this drug

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

- Name of laboratory test
- Site reference value
- Unit
- Date of measurement
- Test results

8.4. Data sources

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

8.5. Study size

8.5.1. Sample size

A total of 300 patients will be included in the safety analysis set (SAS).

8.5.2. Rationale

The number of patients with ATTR-CM in Japan is estimated to be approximately 750. Of these, the proportion of patients who actually received the definitive diagnosis and were prescribed with this drug was estimated to be approximately 40% (approximately 300 patients). As a result, the target sample size was set at 300 subjects from the viewpoint of feasibility. The target sample size of 300 subjects was comparable to the active drug group (264 patients) in the global phase 3 study, and from this point of view, it is considered possible to confirm the safety and effectiveness of the drug to some extent.

If the number of subjects in the SAS is 300, at least 10 subjects with hepatotoxicity can be observed with a probability of approximately 98%, assuming that the true incidence of hepatotoxicity with the lowest incidence based on Studies B3461028 and B3461045 is 5.88% for infections, hypersensitivity reactions, and hepatotoxicity, all of which are important potential risks that can be reviewed.

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 either a paper form or an electronic data record, or both, depending on the data collection method used in this study.

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

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

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

8.6.2. Record retention

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

8.6.3. Data collection method (EDC)

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

8.6.4. Patient registration (EDC)

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

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

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

8.6.5.1. Data entry

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

8.6.5.2. Data revision

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

8.6.5.3. Submission

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

8.6.6. Data collection method (paper CRFs)

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

8.6.7. Patient registration (paper CRFs)

The investigator will complete the registration form provided by Sponsor for patients receiving this drug and submit the form to Patient Registration Center via FAX. Patient registration will be performed immediately after the first administration of this drug.

1. After the patient was registered, "the notification of the patient registration" will be sent by FAX. Investigator will maintain the notification at the site.

2. If information in the registration form require confirmation, the investigator may be requested to perform follow-up survey. For follow-up survey, "follow-up survey request form" and "registration form (copy)" will be sent from the Registration Center to the investigator by FAX.

8.6.8. Points to consider for completion, revision, and submission of CRF (paper CRFs)

8.6.8.1. Data entry

The investigator should confirm the survey items, complete the CRF based on medical records and other medical records such as relevant test results, using an ineffaceable ink such as ballpoint pen.

8.6.8.2. 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 resubmit the form.

8.6.8.3. Submission

After data entry and revision are completed, CRFs should be submitted by the investigator to the designated address following confirmation of entry and follow-up survey.

8.6.9. All cases survey registration

1. The investigator will confirm whether all patients receiving this drug before 31 March 2021 are registered. The investigator should sign and affix a seal to the all-cases survey confirmation sheet and submit it to the site staff. E-mail etc. can be also used.

2. Any unregistered patients should be promptly registered.

8.7. Data analysis

1. Definition of analysis set

The SAS consists of a full analysis set (FAS) that is as closer as possible to all patients who received this drug. The effectiveness analysis set consists of patients included in the SAS considered evaluable for efficacy. The details will be described in the separately prescribed Statistical Analysis Plan (SAP). Safety and effectiveness should be evaluated using all data collected during the observation period without classifying the data into Vyndaqel and Vynmac unless otherwise specified.

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.

Based on the above method, important missing information and important potential risks will also be evaluated.

- Analysis for effectiveness evaluation

Time course of changes in the following items from the start of administration of this drug will be recognized.

- NYHA Functional Classification

- Cardiac biomarker values (NT-pro BNP, BNP, troponin I, and troponin T)

In addition, survival time analysis will be performed using survival information obtained up to 30 months after the start of administration.

- Subset analysis

The analysis by variant genotype and NYHA Functional Classification will be also performed for the above safety and effectiveness evaluations.

Also, the onset status of adverse reactions will be evaluated for each product (Vyndaqel or Vynmac) during the treatment period until the first switching to Vynmac for Vyndaqel and during the treatment period after the first switching to Vynmac for Vynmac.

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 plans outlined in the full protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a full protocol amendment.

8.8. Quality control

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

8.9. Limitations of the research methods

There may be potential limitations in this study:

1. Since no control group is included in the study, there is a limitation in determining whether or not a risk of developing adverse events and adverse reactions increases with administration of this drug.
2. Due consideration may not be given to confounding factors due to insufficient background information collected.
3. Since this study collects the information described in medical records, specified data may not be collected or may be missing.

8.10. Other 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. If these information falls under personal information of the Personal Information Protection Act, these actions may not be based on the laws or regulations, and therefore, may correspond to provision to the third party and using the information for purposes other than business that require consent from the patient. Therefore, the study institutions will obtain written or verbal consent from the patients to be included in this study so that Pfizer can use the results of this study to report to Pfizer Inc., group companies or regulatory authorities in other countries, or to present it at academic conferences or publish manuscript, etc. Whether consent is obtained from patients or not is described in the CRF. The original of the written informed consent form should be retained by the study investigator.

In general, the investigator must obtain consent from a patient personally. However, if the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted or he or she is a minor, consent is obtained from legally acceptable representative or parent(s) or legal guardian if the patient is a minor. 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) or legal guardian if the patient is 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)/Ethics Committee (EC)

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

9.4. Ethical conduct of the study

This study will be conducted in compliance with the MHLW Ordinance in the section 6. RATIONALE AND BACKGROUND. Also, the study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1. Requirements

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

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

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (refer to section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to this drug**. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.
For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

10.2. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of this drug, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of

the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to this drug, the SAE also must be reported to Pfizer Safety.

10.3. Causality assessment

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

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

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

10.4. Definitions of safety events

10.4.1. Adverse events

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

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

- Drug dependency.

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

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

Abnormal test findings

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

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

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

10.4.2. Serious adverse events

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

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

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

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

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

Hospitalization

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

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

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)

Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

10.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

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

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

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

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

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

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

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

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

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

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

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE [e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly (in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death)], the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

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

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

Exposure during breastfeeding

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

Medication error

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

Medication errors include:

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

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

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

- An identifiable reporter;
- A suspect product;
- The event medication error.

Overdose, Misuse, Extravasation

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

Lack of Efficacy

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

Occupational Exposure

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

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

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

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

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

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

Company name: Medidata Solutions
Address: 2-7-2, Marunouchi, Chiyoda-ku, Tokyo
Scope of work contracted: Works related to establishment and operation of EDC

Company name: A2 Healthcare Corporation
Address: 1-4-1, Koishikawa, Bunkyo-ku, Tokyo
Scope of work contracted: Reception work for registration, work of CRF transfer, work of EDC account management, etc.

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

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

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

1. Review the necessity for changing the contents of this study plan including the presence or absence of new safety specifications.

2. Review the necessity for formulating risk minimization measures for new safety specifications.

14. SCHEDULED TIMING OF MILESTONES FOR EVALUATING IMPLEMENTATION STATUS AND OBTAINED RESULTS OR REPORTING TO THE PMDA, AND THEIR RATIONALES

At the time of Periodic Safety Update Reports and the final evaluation of all-cases survey. To make a comprehensive review of the safety information.

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

16. CONTACT INFORMATION

16.1. Contact information for inquiries about the study

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

16.2. Contact information for inquiries about the EDC system (For the study using the EDC)

Name	Medidata Helpdesk
Business Hours	9:00 to 20:00 on weekdays (except Saturdays, Sundays, national holidays, and year-end and New Year holidays)
TEL	PPD (Pfizer dedicated dial)
E-mail address	japanhelpdesk@mdsol.com

17. REFERENCES

None

18. LIST OF TABLES

- Page 16.

  Table 1. Variables and schedule of activities

- Page 19.

  Table 2. NYHA Functional Classification

19. LIST OF FIGURES

- Page 14.

  Figure 1. Observation period for each booklet

- Page 14.

  Figure 2. Setting of observation period for transferred patients

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable

TRANSLATION RECORD (FOR POST-MARKETING SURVEILLANCE STUDY IN JAPAN)	10-Jan-2019

Document Type	B3461064 Non-English text ver 8		
Document Date (Original)	24 Oct 2023		
Program	B346	**Study**	B3461064
Original Language	Non-English text	**Site**	NA
Translation Language	Non-English text	**Is a back translation required?**	NO

FULL TRANSLATION AND REVIEW INFORMATION

Translator Qualification Type	Translation vendor		
Translation Vendor	Honyaku Center		
Translator Name	Honyaku Center	**Date of Translation**	26 Jun 2025
Reviewer Name	PPD	**Date of Review**	03 Jul 2025