(Appendix)

Vyndaqel Capsules Special Investigation

- Investigation on long-term use -

Protocol

Pfizer Japan Inc.

[redacted]

STUDY INFORMATION

Title	Vyndaqel Capsules Special Investigation - Investigation on long-term use -
Protocol number	B3461042
Protocol version identifier	5.0
Date of last version of protocol	1 December 2018 (Ver. 4.0)
Active substance	Tafamidis meglumine
Medicinal product	Vyndaqel® Capsules 20 mg
Research question and objectives	To comprehend information on the safety (e.g., onset status of adverse reactions) and efficacy of this drug in the long-term use under the post-marketing actual use in all patients receiving this drug. Review on the onset status of hepatotoxicity will be set as a major investigation item in this study. <<Conditions for approval: Because the number of study participants in Japan is very limited, a drug use investigation in all patients should be conducted during the reexamination period to grasp the background information on patients using this drug, collect data on the safety and efficacy of this drug early, and take necessary measures for proper use of this drug.>>
Author	PPD Post Marketing Study Strategy and Management PMS Planning & Operation Group 1

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1. LIST OF ABBREVIATIONS

Acronym	Title
AE	Adverse event
ALT	Alanine transaminase
AL-P	Alkaline phosphatase
AST	Aspartate transaminase
EDP	Exposure during pregnancy
FT4	Free thyroxine
GOT	Glutamic oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
γ-GTP	γ-glutamyl transpeptidase
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDH	Lactate dehydrogenase isozyme
mBMI	modified body mass index
N/A	Not applicable
NIS	Non interventional study
NIS	Neuropathy Impairment Score
QOL	Quality of life
QOL-DN	Quality of Life-Diabetic Neuropathy
SAE	Serious adverse event
T4	Thyroxine
THAOS	Transthyretin-Associated Amyloidosis Outcomes Survey
TTR	Transthyretin
TTR-FAP	Transthyretin familial amyloid polyneuropathy
SRSD	Single Reference Safety Document
TSH	Thyroid-stimulating hormone

2. RESPONSIBLE PARTIES

The Good Post Marketing Study Practice officer

Principal Investigator(s) of the Protocol
N/A

[redacted]

3. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendments	Reason
5.0	28 March 2019	Amendment of the investigated contents	Sections 7.2.4, 7.3.2.10, 7.3.2.13, 8.2	If the dose of Vyndaqel is changed for the treatment of ATTR-CM, the investigation will be discontinued.	Since the special investigation of ATTR-CM (all-cases survey) will be conducted in association with the added indication of ATTR-CM, the withdrawal criteria for the investigation were set in order to prioritize registration to the investigation on major diseases for treatment.
		Other amendment(s)	Section 7.6	Additional descriptions of Sections 7.6.1 and 7.6.2 and improvement of descriptions of Section 7.6.5.2 accordingly	Additional descriptions due to amendment of a company template and improvement of descriptions accordingly, which will not affect the contents of investigation. Because the contents of descriptions were reexamined and improved.
		Other amendment(s)	Sections 8 and 9	Update of contents of descriptions	Amendment due to the amendment of a company template, which will not affect the contents of investigation.
		Other amendment(s)	All	Change of wording without change of meaning such as correction of errors in writing and unification/change, etc. of terms	Because the contents of descriptions were reexamined and improved.
4.0	1 December 2018	Other amendment(s)	Study items	Correction of errors in writing	Because of errors in writing

[redacted]

		Other amendment(s)	Definitions of safety events	The definition of "discontinuation of treatment" was changed to "drug withdrawal".	Due to reexamination of Japanese translation
		Other amendment(s)	NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Addition of a contractor	Addition as a result of establishment of Pfizer R&D Japan G.K.
		Other amendment(s)	CONTACT INFORMATION	Change of the company name	Change as a result of establishment of Pfizer R&D Japan G.K.
3.0	19 May 2017	Amendment of the planned contents	Study items	Addition of "confirmation of survival"	Because it was necessary to confirm the survival status
		Other amendment(s)	Registration items	Addition of "Presence or absence of having received/used Vyndaqel at other sites, and if Yes, patient's duration of treatment (name of the site if the treatment period is 3 years or longer)"	Because patients who have received/used Vyndaqel at other sites for more than 3 years are not subject to this study
		Other amendment(s)	Study items	Change in the timing of evaluation of physical symptoms	Because there was inconsistency with the CRF
		Other amendment(s)	Observation period	The observation period for subjects who discontinued the treatment was clearly stated.	Because the observation period was accurately described
		Other amendment(s)	Planned period of investigation	It was described as "the transition to registration only after the registration period will be implemented after consultation with the PMDA".	Added as instructed by PMDA

[redacted]

		Other amendment(s)	All	Correction of errors in writing	Because of errors in writing
2.0	10 August 2015	Other amendment(s)	All Adverse events	Response to a new company form	The form used in the company was changed and the description of requirements for reporting of adverse events which had been handled as Appendix was added to the text, and other items to be described were added. Therefore, a new form was applied.
		Other amendment(s)	Observation period	The definition of patients whose observation period is 1.5 years was changed from "Patients registered after May 2018" to "Patients who started to receive Vyndaqel after May 2018".	The definition of patients with the observation period of 1.5 years was accurately described.
1.1	7 November 2013	Other amendment(s)	Patient registration	Additional description of FAX number of Patient Registration Center	Because new information was obtained
1.0	8 October 2013	N/A	N/A	N/A	N/A

4. MILESTONES

Milestone	Planned date
Start of data collection	November 2013
End of data collection	May 2021
Final study report	To be determined

5. RATIONALE AND BACKGROUND

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare, highly heritable disease in which amyloid derived from transthyretin (TTR) is deposited in the peripheral and autonomic nervous systems, thereby causing dysfunction. In Japan, patients are accumulated in Nagano and Kumamoto prefectures. It is known that the onset of the disease in the accumulated area is young in the 30s and the duration of survival after the onset is approximately 10 years, which is extremely poor prognosis. However, the only treatment for TTR-FAP in Japan has been symptomatic treatment for each of the various symptoms associated with the disease. Liver transplant has been performed as the only method to suppress the

[redacted]

disease progression, but the target patients for liver transplant are very limited due to problems such as lack of donors and risk of transplant surgery.

Vyndaqel (generic name: tafamidis meglumine) is a therapeutic agent for TTR-FAP with a novel mechanism of action that suppresses amyloid formation by binding to the thyroxine (T4) binding site of the TTR tetramer, stabilizing the TTR tetramer, and inhibiting its dissociation into monomers. The overseas clinical studies started in 2007 demonstrated the efficacy of Vyndaqel not only in delaying the progression of peripheral neuropathy, suppressing the decline of quality of life (QOL) and improving nutritional condition in patients with TTR-FAP but also in stabilizing TTR early after the start of treatment and maintaining TTR stabilization throughout the study period. As a result, Vyndaqel was approved in Europe in November 2011 and has been in the market. In Japan, the phase 1 study confirmed no difference in pharmacokinetics, TTR stabilization, and safety between Japanese and non-Japanese subjects. Furthermore, the domestic phase 3 clinical study in Japanese adult patients with TTR-FAP also demonstrated the efficacy and safety of Vyndaqel equivalent to those in the results of the overseas clinical studies. As a result, the application for approval was filed in February 2013 and the drug was approved in September 2013.

The Special Investigation of Vyndaqel Capsules - Investigation on long-term use - (hereinafter referred to as this study) will be conducted to comprehend information on the safety (e.g., onset status of adverse reactions) and efficacy of Vyndaqel in the long-term use under the post-marketing actual use in patients receiving Vyndaqel Capsules (hereinafter referred to as this drug). This study will be conducted in all patients receiving this drug on the basis of the conditions for approval. The information collected in this study will be used to provide information on proper use and prepare application dossiers for reexamination. Therefore, this study must be conducted in strict compliance with the “Ordinance Concerning Standards for Conducting Post-Marketing Study and Studies on Pharmaceutical Products” (MHLW Ordinance No. 171 dated December 20, 2004). The case data collected in this study will be reported to the Ministry of Health, Labour and Welfare (MHLW) according to the Pharmaceuticals and Medical Devices (PMD) Act. In this case, the data may also 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 information on names of drugs, adverse reactions, gender, and age (increment of 10 years). 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 any form or shape.

6. RESEARCH QUESTION AND OBJECTIVES

To understand information on the safety (e.g., onset status of adverse reactions) and efficacy of this drug in the long-term use under the post-marketing actual use in all patients receiving this drug. Review on the onset status of hepatotoxicity will be set as a major investigation item in this study.

[Conditions for approval]

Because the number of study participants in Japan is very limited, a drug use investigation in all patients should be conducted during the reexamination period to grasp the background information on patients using this drug, collect data on the safety and efficacy of this drug early, and take necessary measures for proper use of this drug.

[redacted]

6.1. Safety specifications
[Important potential risks] Hepatotoxicity, hypersensitivity reaction, reproductive and developmental toxicity, infection
[Important missing information] Patients with severe hepatic impairment

7. RESEARCH METHODS

7.1. Study design
This study is a multi-center, cohort study of patients receiving/using this drug. The investigators complete the case report form (CRF) based on the information extracted from the medical charts created in daily medical practice.

7.2. Setting
All patients who received/used this drug will be targeted in this study.

The indication, dosage and administration, and contraindications of this drug are as follows. When using this drug, refer to the latest package insert of this drug.

[Indication] Suppression of progression of peripheral neuropathy in transthyretin familial amyloid polyneuropathy (TTR-FAP)

[Dosage and administration] The usual adult dosage for oral use is 20 mg of tafamidis meglumine once daily.

[CONTRAINDICATIONS] Patients with a history of hypersensitivity to any of the ingredients of this drug

7.2.1. Sites for this study
This study will be conducted at all sites and medical departments that use this drug.

7.2.2. Duration of study
The planned period covered by this study is as follows.
Duration of study: November 2013 to May 2021 (7.5 years)
Registration period: November 2013 to November 2019 (6 years)
A contract will be concluded after the start date of the study period, and then, the patient registration will be started. The transition to registration only after the registration period will be implemented after consultation with the Pharmaceuticals and Medical Devices Agency (PMDA).

7.2.3. Study procedures

7.2.3.1. Study method
This study will be conducted by all-cases survey (including retrospective survey).

7.2.4. Observation period
3 years from the first day of treatment with this drug (156 weeks)
However, the observation period for patients who started to receive this drug after May 2018 will be 1.5 years (78 weeks).

[redacted]

If the treatment with this drug is discontinued during the observation period, the observation period will be until the day of discontinuation. If the dose of this drug is changed for the treatment of ATTR-CM, the observation period will be up to the date of last dose of 20 mg.
This study will be conducted using booklet type CRF.
The safety and efficacy assessments will be performed at the first visit (including the end date of the observation period) on or after the end date of the observation period (day of discontinuation if the treatment is discontinued during the observation period or date of the last dose of 20 mg if the dose was changed for the treatment of ATTR-CM). However, if a subject is lost to follow-up halfway through, the safety and efficacy assessments will be performed using the information on the last visit date.

Booklet No.	Observation period
Booklet 1	First day of treatment to Week 78 (1.5 years)
Booklet 2	Week 79 to Week 156 (3 years)

[redacted]

7.3. Registration items and study items

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

Table 1. Schedule of observation

Item	Registration form	Booklet 1			Booklet 2	
		At start of the study	Week 52 (1 year)	Week 78 (1.5 years)	Week 104 (2 years)	Week 156 (3 years)
Information to identify the subject	●	●	-	-	-	-
First day of treatment with this drug	●		-	-	-	-
Presence or absence of having received/used this drug at other sites, and if Yes, patient's duration of treatment	●					
THAOS registration status/THAOS registration ID	●	←	—	—	—	→
State of concurrent medical examination	-	←	—	—	—	→
Background variables	-	●	-	-	-	-
History of previous treatment drugs for the targeted disease	-	●	-	-	-	-
Targeted drug use record	-	←	—	—	—	→
Concomitant therapy (drug therapy/ non-drug therapy)	-	←	—	—	—	→
General tests (height, body weight, pulse, blood pressure)	-	←	—	—	—	→
Clinical laboratory tests	-	←	—	—	—	→
Plasma concentration of tafamidis (to be performed only for patients with severe hepatic impairment)	-	←	—	—	—	→
Cardiovascular evaluation (ECG, echocardiography)	-	←	—	—	—	→
Assessment of neurological function (NIS)	-	●	-	●	-	●
Quality of Life (QOL-DN)	-	●	-	●	-	●
Ambulatory state	-	●	-	●	-	●
Neurological assessment (motor function, tendon reflex, tactile sense, pain sensation, vibration sense, positional sense)	-	●	●	-	●	●
Medical assessment of physical symptoms	-	←	—	-	—	→
Pregnancy	-	←	—	—	—	→
Record of study discontinuation	-	←	—	—	—	→
Confirmation of description concerning adverse events corresponding to major investigation item	-	←	—	—	—	→
Adverse events and tests for adverse events	-	←	—	—	—	→
Confirmation of survival						●

[redacted]

7.3.1. Registration items

Enter the following information at the start of treatment with this drug in the registration form. The day when the treatment with this drug is started will be defined as "first day of treatment". However, for subjects who participated in the clinical studies (including post-marketing clinical studies), the day when the treatment with a commercially available product of this drug is started will be defined as "first day of treatment". For patients who have received/used this drug at other sites, the day when the treatment is started at the own site will be defined as "first day of treatment"*. However, if the drug is prescribed at another site and only the diagnosis of TTR-FAP is made at the own site, the day when the treatment with this drug is started at another site will be defined as "first day of treatment".

*If the patient has been receiving this drug for more than 3 years at the first day of treatment with this drug at the own site and the name of the site is known, only the patient registration will be made.

(1) Name of site/department
(2) ID number
(3) Gender
(4) Date of birth (age at the start of treatment with this drug at the site if the information cannot be disclosed)
(5) First day of treatment with this drug
(6) Presence or absence of having received/used this drug at other sites, and if Yes, patient's duration of treatment (name of the site if the treatment period is 3 years or longer)
For sites participating in THAOS** at the time of registration, the following information should also be entered:
(1) THAOS registration status
(2) THAOS case number
**THAOS (Transthyretin-Associated Amyloidosis Outcomes Survey) is a multinational disease registry of all patients with TTR-associated amyloidosis (hereinafter referred to as ATTR) and participants who are not diagnosed with ATTR but have TTR mutations.

7.3.2. Study items

Enter the following information in CRF.

7.3.2.1. Information to identify the subject

(1) ID number
(2) Gender
(3) Date of birth (age at the start of treatment with this drug at the site if the information cannot be disclosed)

For sites participating in THAOS within the observation period, the following information should also be entered:

(1) THAOS registration status
(2) THAOS case number

7.3.2.2. State of concurrent medical examination

Regarding the status of concurrent medical examination after the start of treatment with this drug until the end of observation period, enter the following information:

(1) Prescription of this drug or treatment of the target disease at sites other than this hospital

[redacted]

(2) If Yes for concurrent medical examination, name of site

7.3.2.3. Patient characteristics

Enter the following information at the start of treatment with this drug.

(1) Experience of treatment with this drug
(2) Classification of inpatient/outpatient
(3) Target disease and onset timing
(4) Diagnosis of TTR amyloidosis
(Mutant genotype and timing of identification, diagnostic method [including the conduct of tissue biopsy], Karnofsky index*)
(5) Family history of TTR-FAP
(6) Classification of accumulated cases/non-accumulated cases
Enter the classification of accumulated/non-accumulated area as the patient's birthplace.
In this study, Nagano, Kumamoto, and Ishikawa prefectures are defined as accumulated areas.
(7) History of organ transplant (timing of transplant, name of transplanted organ [including the presence or absence of liver transplant and its timing])
(8) Presence/absence and severity of hepatic/renal impairment
If "Yes" for hepatic impairment, enter the reason for judgment of severity.
(9) Medical history (past history/complications)

Table 2. Karnofsky index

*Karnofsky index (Karnofsky Performance Status) (%)[2)–8)]	
100 :	Normal; no complaints; no evidence of disease.
90 :	Able to carry on normal activity; minor signs or symptoms of disease.
80 :	Normal activity with effort; some signs or symptoms of disease.
70 :	Cares for self; unable to carry on normal activity or to do active work.
60 :	Requires occasional assistance, but is able to care for most of their personal needs.
50 :	Requires considerable assistance and frequent medical care.
40 :	Disabled; requires special care and assistance.
30 :	Severely disabled; hospital admission is indicated although death not imminent.
20 :	Very sick; hospital admission is necessary although death not imminent.
10 :	Moribund; fatal processes progressing rapidly.
0 :	Dead

7.3.2.4. Previous treatment drugs

Enter all drugs used for the treatment of the target disease from 24 weeks before the start of treatment with this drug until the day before the first day of treatment (including NSAIDs).

(1) Drug name, dosage form
(2) Dose and frequency of daily dose
(3) Duration of treatment
(4) Reason for discontinuation

[redacted]

7.3.2.5. Pregnancy

If the patient is female, enter the presence or absence of pregnancy (if she is pregnant, date of delivery or expected date of delivery) from the first day of treatment with this drug until the end of observation period (or date of discontinuation of treatment with this drug) in each booklet.

7.3.2.6. Targeted drug use record

Enter the following information on the status of using this drug from the first day of treatment with this drug until the end of observation period (or date of discontinuation of treatment with this drug).

(1) Dose
(2) Frequency of daily dose
(3) Duration of treatment
(4) Reason for change/washout

7.3.2.7. Concomitant therapy

7.3.2.7.1. Drug therapy

For all drugs used from the first day of treatment with this drug until the end of the observation period (or date of discontinuation of treatment with this drug), enter the information on administration (e.g., name of drug [product name], route of administration, dose, duration of treatment, and presence or absence of any action taken for adverse events). Also, enter drugs administered for the treatment of adverse events.

7.3.2.7.2. Non-drug therapy

For all non-drug therapies provided from the first day of treatment with this drug until the end of the observation period (or date of discontinuation of treatment with this drug), enter the name of therapy, implementation period, and presence or absence of any action taken for adverse events. Also, enter therapies provided for the treatment of adverse events.

7.3.2.8. Tests/clinical laboratory tests

For the following test items conducted from the first day of treatment with this drug until the end of the observation period (or date of discontinuation of treatment with this drug), enter the test dates (dates of measurement) and test results. For the tests conducted before the start of treatment with this drug, enter the test results immediately before the first day of treatment (including the first day of treatment). For clinically significant fluctuations compared to those before the start of treatment with this drug, enter the details in the adverse event column.

7.3.2.8.1. Clinical laboratory tests

(1) Hematology: White blood cell count, neutrophil count, lymphocyte count, red blood cell count, platelet count, hemoglobin, prothrombin time
(2) Biochemistry: AST (GOT), ALT (GPT), AL-P, LDH, γ-GTP, total bilirubin, triglycerides, serum creatinine, serum albumin
(3) Endocrine test: Thyroid-stimulating hormone (TSH), total T4, free thyroxine (FT4)
(4) Urinalysis: Urine protein (qualitative)

[redacted]

7.3.2.8.2. General tests

(1) Height
(2) Weight
(3) Pulse
(4) Blood pressure (systolic/diastolic)

7.3.2.8.3. Plasma concentration of tafamidis (to be performed only for patients with severe hepatic impairment)

If the patient has severe hepatic impairment, measure the plasma concentration of tafamidis as much as possible and enter the following information. If the patient has hepatic function disorder at the start of treatment with this product, enter the details in the section of "Presence or absence of hepatic/renal impairment" and if it occurred during the observation period, enter the details in the section of "Adverse Events". If a laboratory test related to hepatic impairment is performed, enter the test results in the section of "Laboratory tests" or the section of "Tests for adverse events".
For the detailed method of measuring plasma concentration of tafamidis, refer to the Appendix to Guidelines for Special Investigation "Procedures for Measurement Plasma Concentration of Tafamidis in Patients with Severe Hepatic Impairment" (Appendix 1).

(1) Record of medicines immediately before blood sampling (date and time of medicines)
(2) Record of blood sampling (date and time of blood sampling)
(3) Plasma concentration of tafamidis

Table 3. Child-Pugh Classification

*Overseas clinical studies were conducted by defining moderate hepatic impairment as Child-Pugh score of ≤9.
[Reference: Child-Pugh classification] The scores for each item are totaled and 5 to 6 points are classified as A, 7 to 9 points as B, and 10 to 15 points as C.

[Child-Pugh classification]	1 point	2 points	3 points
Hepatic encephalopathy	None	Mild	Occasional coma
Ascites	None	Small amount	Moderate amount
Total serum bilirubin (mg/dL)	<2.0	2.0-3.0	3.0<
Serum albumin (g/dL)	3.5<	2.8-3.5	<2.8
Prothrombin time (%)	70<	40-70	<40

7.3.2.8.4. Cardiovascular assessment

(1) Standard 12-lead ECG
(2) Echocardiography

7.3.2.8.5. Assessment of neurological function (NIS)

Enter scores for the following (1) to (4) items according to the assessment indicators for neurological function shown below by using Neuropathy Impairment Score (NIS)[9].

[Timing of assessment] Before the start of treatment (results immediately before treatment including the first day of treatment), Week 78 (1.5 years later), Week 156 (3 years later) (or at discontinuation of treatment with this drug)

[redacted]

(1) Cranial Nerves: Items 1 to 5
(2) Muscle Weakness: Items 6 to 24

Cranial nerves and muscle weakness will be graded on the following 8-point scale:
0 = Normal
1 = 25% Weak
2 = 50% Weak
3 = 75% Weak
3.25 = Move against gravity
3.5 = Movement, gravity eliminated
3.75 = Muscle flicker, no movement
4 = Paralysis

(3) Reflexes: Items 25 to 29
(4) Sensation: Index finger (items 30 to 33), great toe (items 34 to 37)

Tendon reflexes (reflexes) and sensation of index and great toes (sensation; tactile sense, pain sensation, vibration sense, joint sense) will be graded on the following 3-point scale:
0 = Normal
1 = Decreased
2 = Absent

7.3.2.8.6. Quality of life (QOL)

The QOL will be assessed using Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN)[10), 11)]. Norfolk QOL-DN is a self-completed assessment scale for patients with neuropathy that can quantify the impact of neuropathy on QOL. This scale consists of 35 questions, each of which relates to the following functions and symptoms:

TQOL score, physical function/large nerve fiber disorder score, activities of daily living score, symptom score, small nerve fiber disorder score, autonomic neuropathy score

For data collection, the Norfolk QOL-DN questionnaire (Appendix 2) will be used to answer all questions by the patient himself or herself as much as possible. The investigator will complete the study items by referring to the questionnaires.

[Timing of assessment] Before the start of treatment (results immediately before treatment including the first day of treatment), Week 78 (1.5 years later), Week 156 (3 years later) (or at discontinuation of treatment with this drug)

7.3.2.8.7. Ambulatory status

Ambulatory status will be assessed using the ambulatory ability scale in the polyneuropathy dysfunction score.

[redacted]

[Timing of assessment] Before the start of treatment (results immediately before treatment including the first day of treatment), Week 78 (1.5 years later), Week 156 (3 years later) (or at discontinuation of treatment with this drug)

Walking ability rating scale
0: Good
1: Able to walk without difficulty despite of sensory disorder in the lower extremities
2: Able to walk without assistance despite of some difficulties
3a: Able to walk with one stick or crutch
3b: Able to walk with two sticks or crutches
4: Unable to walk, restricted to wheelchair or bedridden

7.3.2.8.8. Neurological assessment

Enter the test results for the following neurological assessments (1) to (6). The observation period is defined as follows and, if the observation period is discontinued, enter the test results at the time of discontinuation as much as possible.

[Timing of assessment] Before the start of treatment (results immediately before treatment including the first day of treatment), Week 52 (1 year later), Week 104 (2 years later), Week 156 (3 years later) (or at discontinuation of treatment with this drug)

(1) Motor
The motor will be assessed using a Medical Research Council (MRC) Scale.

Medical Research Council Scale (MRC)	MRC Scale[12)]
0	No contraction
1	Flicker contraction
2	Muscle contraction with active motion with gravity eliminated
3	Full range of motion against gravity
4	Full range of motion against gravity with some resistance
5	Full range of motion against gravity with maximum resistance for that muscle

(2) Reflexes

Reflexes will be assessed with the following items:
Present, Absent

(3) Light Touch
(4) Pin Prick
(5) Vibration
(6) Position Sense

[redacted]

Light touch, pin prick, vibration, and position sense will be assessed with the following scales: Normal, Decrease, and Absent

7.3.2.9. Medical assessment of physical symptoms

The following diseases or syndromes will be confirmed for the presence or absence, time of onset/disappearance, relationship with ATTR, severity*, etc.

[Timing of assessment] At the start of treatment (results immediately before treatment) to the end of observation period or at discontinuation of treatment with this drug

*Follow the following classification for the assessment of severity.
1: Mild
The symptom is mild and usually transient. It may require short-term treatment (drug or non-drug therapy) but does not limit the patient's daily activities.
2: Moderate
The symptom is moderate. The symptom may require continuous treatment (drug, special treatment) and limit the patient's daily activities. In most cases, the patient is capable of self-care, but may require occasional assistance or other procedure (hospitalization or medical procedure).
3: Severe
The symptom is severe. Severe symptoms may be transient but are accompanied by marked disability or pain. They require treatment (drug therapy or hospitalization) and special assistance to improve symptoms. Severe symptoms may be progressive and/or life-threatening and require further treatment to maintain the patient's condition, although improvement of symptoms cannot be expected.

(1) Neurologic
(2) Eye
(3) Cardiovascular

Follow the following classification for the severity of heart failure:

[NYHA Grade	New York Heart Association Classification]
Class I:	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II:	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.
Class III:	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV:	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(4) Genitourinary/Renal/Reproductive
(5) Gastrointestinal
(6) Endocrine/Metabolic
(7) Musculoskeletal
(8) Respiratory

[redacted]

(9) Psychiatric

7.3.2.10. End-of-study (discontinuation) record

Confirm whether or not treatment can be continued by this drug during the observation period. If treatment with this drug cannot be continued or if the study is discontinued because the dose of this drug was changed for the treatment of ATTR-CM, enter the date of the last visit (date of the last dose of 20 mg if the dose of this drug was changed for the treatment of ATTR-CM) and reason for discontinuation. If an adverse event was selected as the reason for discontinuation, enter the detailed information in the adverse event column.

(1) Date of the last visit (date of the first visit after the last dose of this drug)
(2) Reason for discontinuation

7.3.2.11. Effectiveness evaluation

The following 10 items should be evaluated for effectiveness:

(1) NIS (See Section 7.3.2.8.5.)
Evaluate the NIS total score, the NIS Upper Limb (NIS-UL) total score, the NIS Lower Limb (NIS-LL) total score, scores of cranial nervous system (sum of items 1 to 5), muscle weakness (sum of items 6 to 24), tendon reflex (sum of items 25 to 29), and sensation (index finger: sum of items 30 to 33, great toe: sum of items 34 to 37).
(2) Norfolk QOL-DN (See Section 7.3.2.8.6.)
Evaluate the TQOL scores (sum of all 35 items) and 5 domain scores (physical function/large nerve fiber disorder score, activities of daily living score, symptom score, small nerve fiber disorder score, and autonomic neuropathy score).
(3) Modified Body Mass Index (mBMI)
mBMI is calculated by multiplying BMI by serum albumin level.
(4) Ambulatory status (ambulatory ability scale in polyneuropathy dysfunction score)
Evaluate the ambulatory status (see Section 7.3.2.8.7 for details).
(5) Motor
Evaluate the motor function with MRC (16 items in total) (see Section 7.3.2.8.8 for details) scale.
(6) Reflexes
Evaluate the tendon reflexes (5 items in total) (see Section 7.3.2.8.8 for details).
(7) Light Touch
Evaluate the tactile (11 items in total) (see Section 7.3.2.8.8 for details).
(8) Pin Prick
Evaluate the pain sensation (11 items in total) (see Section 7.3.2.8.8 for details).
(9) Vibration
Evaluate the vibration sense (6 items in total) (see Section 7.3.2.8.8 for details).
(10) Position Sense
Evaluate the positional sense (4 items in total) (see Section 7.3.2.8.8 for details).

7.3.2.12. Adverse events

Occurrence of adverse events (AEs) from the start date of administration of this drug to the end date of observation period should be confirmed and the following information should be recorded. If any AE is

observed, the investigator will take appropriate measures, promptly report it to Pfizer, and in principle, transcribe and confirm the course until the symptom disappears.
Also, further investigation should be separately conducted, if deemed necessary by Sponsor for patients who experienced a serious adverse reaction, an unexpected adverse reaction or other adverse reactions not listed in the package insert.

(1) Presence/absence of AE
(2) Name of AE
(3) Date of occurrence
(4) Intervention
(5) Seriousness
(6) Outcome
(7) Causal relationship to this drug

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

(1) Laboratory parameter
(2) Site reference value
(3) Unit
(4) Date measured
(5) Results

Note: AEs are any and all unfavorable events (including clinically significant abnormal changes in laboratory tests) occurring in patients after starting the targeted drug treatment regardless of their causal relationship. Serious adverse events (SAEs) are any unfavorable medical occurrences that result in death, are life-threatening, require (or prolong) hospitalization, cause persistent or significant disability/incapacity, result in congenital anomalies or birth defects, or are other conditions which represent significant health hazards.

7.3.2.13. Confirmation of survival

For patients who completed the study, the following information will be entered 3 years after the start of treatment with this drug at the own site for confirmation of survival:

(1) In the case of survival: Date of survival confirmed
(2) In the case of death: Date of death, cause of death (TTR-FAP/other than TTR-FAP)
(If the date of death is unknown, the last date of survival confirmed and the date of information on death obtained)

Among the patients who discontinued the study, their survival will be confirmed using the attached CRF 3 years after the start of treatment for patients who discontinued the study because the reason for discontinuation as follow-up after discontinuation of treatment is other than transfer to another hospital/department, no return to the hospital, or having adverse events resulting in death as outcome and for patients who discontinued the study for the treatment of ATTR-CM.

(1) In the case of survival: Date of survival confirmed
(2) In the case of death: Date of death, cause of death (TTR-FAP/other than TTR-FAP)

[redacted]

(If the date of death is unknown, the last date of survival confirmed and the date of information on death obtained)

(3) If survival or death is unknown: Last date of survival confirmed

For patients who started the treatment with this drug after May 2018 (1.5-year observation period), their survival should be confirmed using the attached CRF 1.5 years after the start of treatment at the own site.

7.3.2.14. Major investigation items

Hepatotoxicity should be evaluated in this study as a major investigation item and, if information on hepatotoxicity is obtained, it will be separately investigated in detail.

[Rationale for setting]
Although necrosis and hypertrophy of hepatocytes were observed in the repeated-dose toxicity study in mice, since the Japanese clinical data at the time of approval application are limited, hepatotoxicity was set as the major investigation item in this study to confirm the post-marketing safety profile.

7.3.2.15. Confirmation of description concerning adverse events corresponding to major investigation item

The investigator will confirm that the AEs corresponding to hepatotoxicity, the major investigation item in this study, have been entered in the AE column.

7.4. Data sources

In this study, the investigators extract the necessary information from the medical record in accordance with the full protocol.

7.5. Study size

7.5.1. Planned sample size

All patients who received/used this drug will be targeted in this study.

7.5.2. Rationale for sample size

On the basis of the review of data on patients with familial amyloid polyneuropathy who were registered in the database from the Amyloidosis Clinical Survey Forms of the Specific Diseases Treatment Research Program by the Ministry of Health, Labour and Welfare for 3 years from 2003 to 2005, it is reported that the number of patients with familial amyloid polyneuropathy is 64 to 88 patients/year, and the estimated prevalence of familial amyloid polyneuropathy in Japan is 0.87 to 1.1 per population of 1 million people after the number of patients was corrected and calculated from the acquisition rate of data[1)] . When this prevalence is multiplied by the Japanese population (127.54 million, as of November 2012), the estimated number of patients with TTR-FAP (hereinafter referred to as this disease) is approximately 111 to 140. On the website of the Japan Intractable Diseases Information Center, the estimated annual number of patients treated for this disease is approximately 130 on the basis of the nationwide epidemiological survey conducted in 1991. As described above, considering that this disease is a rare disease and the safety and efficacy information of this drug based on Japanese clinical studies are limited, all patients who received/used this drug will be collected as much as possible.

[redacted]

7.6. Data management

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

As used in this protocol, the term CRF should be understood to refer to a paper form, 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 paper form and will be 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.

7.6.2. Record retention

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

7.6.3. Data collection method

Registration and study data for this study will be collected and recorded in the registration form and CRFs to be supplied by Pfizer. Investigator will complete (each volume of forms) promptly after (each) observation period and submit them to Pfizer.

7.6.4. Patient registration

7.6.4.1. Procedure of patient registration

The investigator will complete the designated registration form provided by Pfizer after the start of treatment with this drug and send it to Patient Registration Center via FAX.

[Patient Registration Center]
FAX: PPD (Available 24 Hours)
Business hours: 9:00 to 17:00 on Mondays through Fridays [except for national holidays, and New Year holidays (29 December to 4 January)]

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

[redacted]

7.6.4.2. Confirmation of patients registered
During the registration period, Pfizer will confirm with the investigator that all patients have been registered at the study sites conducting the study every year using an “all-cases survey confirmation sheet”.

7.6.5. Reminders concerning completing, revising, and submission of case report form
7.6.5.1. Completing
The investigator will check the study items and complete the CRFs based on consultation records and medical records including the results of various tests using indelible ink such as ballpoint pen.

7.6.5.2. Revising
Upon receiving Pfizer's inquiry on the contents of the CRF (query forms), the investigator will again confirm the contents of consultation records, and as required, correct relevant sections of the CRF and submit it.

7.6.5.3. Confirming
After the entry and revision of the CRFs (or CRFs for resurvey) are fully completed, the investigator will confirm any inadequacies in the study items again and affix the printed name and seal or sign the CRFs.

7.6.5.4. Submitting
The investigator will promptly submit the CRFs to Pfizer upon completion.

7.7. Data analysis
1. Definition of analysis set
The safety analysis set (SAS) consists of all patients who received this drug at least once. The effectiveness analysis set consists of those for whom the effectiveness evaluation was conducted at least once among the SAS. The details will be described in the separately prescribed Statistical Analysis Plan (SAP).

2. Method of analysis
(1) Major analysis for safety evaluation
The occurrence of ADRs and the incidence of ADRs (percentage of patients with AEs for which the causal relationship with this drug cannot be ruled out) will be calculated in the SAS.
(2) Major analysis for effectiveness evaluation
For NIS, QOL-DN, and mBMI, their values and changes from baseline at each time point will be calculated in the effectiveness evaluation set. For ambulatory status, motor function (MRC), tendon reflex, tactile sense, pain sensation, vibration sense, and positional sense, changes from baseline at each time point will be calculated. In addition, survival time analysis will be performed using survival information obtained up to 3 years after the start of treatment.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed and maintained by Pfizer. 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.

7.8. Quality control
The site staff will explain the contents of the protocol, etc. to the investigator prior to the implementation of this study and ask the investigator to prepare a CRF based on medical charts

[redacted]

7.9. Limitations of the research methods

The following matters are considered for this study:

1. Since no control group is set in the study, there is a limit to the judgment on whether or not a risk of developing AEs and adverse reactions increases due to the administration of the study drug.
2. The consideration for confounding factors may not be adequate because the background information may not be sufficiently obtained.
3. Since this is a study that collects the information described in medical charts, the set data may not be collected or there may be missing information.

7.10. Other aspects

N/A

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of 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 (subject) names will be removed and will be replaced by a single, specific, numerical code, in accordance with a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his 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.

8.2. 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.

8.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

In this study, review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) is not required. However, this does not apply if it is required by the rules of the medical institution.

8.4. Ethical conduct of the study

This study will be conducted in 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). Also, the study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor.

[redacted]

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The site staff will request the investigator to report the events that need to be reported within 24 hours at the start of the study and also request the report by regularly visiting the investigator during the study period.
The handling of each event in the case where the investigator becomes aware of any event concerning the safety information should be prescribed as follows:
For an event that needs to be reported to the sponsor within 24 hours, the investigator must report it using the designated "Non Interventional study AE Report Form (hereinafter referred to as "NIS AE Report Form").
The NIS AE Report Form will be handled as part of the case report form.

9.1. 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) SAEs; (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy (EDP) , 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
SAEs	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including EDP, 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 Vyndaqel**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.
For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion.

[redacted]

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.

9.2. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of Vyndaqel , 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 she/he considers the SAE to be related to Vyndaqel, the SAE also must be reported to Pfizer Safety.

9.3. 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 Vyndaqel, 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 vyndaqel caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and she/he cannot determine whether Vyndaqel caused the event, the safety event must be reported within 24 hours.

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

9.4. Definitions of safety events

9.4.1. 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;

[redacted]

- 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;
- EDP;
- Exposure during breastfeeding;
- 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 Pfizer.

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.

9.4.2. 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;

[redacted]

- 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

[redacted]

- 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)

9.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

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

EDP

An EDP occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) Vyndaqel, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Vyndaqel (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 Vyndaqel prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective EDP from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with vyndaqel, 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 Vyndaqel 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).

[redacted]

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 EDP 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.

[redacted]

- 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.

9.5. Single reference safety document

A Single Reference Safety Document (SRSD) refers to a document that contains the information on the known safety profile. The package insert of this product will be the SRSD in this study. Pfizer will evaluate the safety information reported by the investigator during the study period using the SRSD. The investigator will also prescribe the drug and give the drug administration guidance on the basis of the SRSD.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The survey results may be published during scientific meetings, in research paper, etc. for the purpose of providing proper use information, etc.

COMMUNICATION OF ISSUES

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.
In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this study protocol that the investigator becomes aware of.

11. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION

The organizational system for study implementation in this study is equivalent to that for operations of post-marketing study in the risk management plan. The director of the post-marketing study strategy and management will be responsible for post-marketing study.

[redacted]

12. NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS

(1) Contractor

PPD

Company name: PPD

Scope of work contracted:

Works related to planning and drafting of study, operation of study, etc.

(2) Contractor

Address: PPD

Company name: PPD

Scope of work contracted:

Preparation of contract documents for the study, Patient Registration Center, data management, preparation of ledger, etc., operations other than management of post-marketing surveillance in the operations related to this study

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

- Review the risk management plan (RMP) including the following contents at the scheduled timing of milestones.
- Review the necessity for changing the contents of this study plan including the presence or absence of new safety specifications.
- Review the necessity for formulating risk minimization measures for new safety specifications.

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

At the time of Periodic Safety Update Report. To make a comprehensive review of the safety information.

15. OTHER NECESSARY MATTERS

1) Amendment of the 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 protocol will be amended if necessary. Also, the need for amendment of the protocol will be examined and the protocol will be amended even if the partial change in the dosage and administration or indication is approved during the reexamination period (except the case when the reexamination period is newly designated), etc.

2) Actions to be taken for any problem or issue

Revision of the RMP should be considered and, if necessary, the PV activities and risk minimization activities should be taken for the following cases: any serious and unknown adverse reaction is suggested; a significant increase in the frequency of adverse reactions is observed; any problem is found in the safety.

16. CONTACT INFORMATION

16.1. Contact information for the contents of the study

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17. REFERENCES

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18. LIST OF TABLES

19. LIST OF FIGURES

N/A

20. LIST OF STAND ALONE DOCUMENTS

- Appendix 1: Procedures for measurement of plasma concentration of tafamidis in patients with severe hepatic impairment
- Appendix 2: Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) Questionnaires (sample)

21. ADDITIONAL INFORMATION

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