Drug Use Investigation of Selara® Tablets

(An investigation for chronic heart failure)

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

.

Pfizer Japan Inc.

[redacted]

STUDY INFORMATION

Title	Drug Use Investigation of Selara® Tablets (An investigation for chronic heart failure)
Protocol ID	A6141122
Protocol version identifier	Amended Version 1
Date of last version of protocol	28 March 2017
Active substance	Eplerenone
Medicinal product	Selara® Tablets 25 mg/Selara® Tablets 50 mg
Research question and objectives	To confirm the safety of this drug in chronic heart failure (CHF) patients, particularly CHF patients with moderate renal impairment, under actual medical practice.
Author of the protocol	Post-Marketing Study Strategy and Management Division Study Strategy and Management Promotion Group 1 PPD

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	*Adverse event*

[redacted]

Al-P	*Alkaline phosphatase*
BNP	*brain natriuretic peptide*
BUN	*Blood urea nitrogen*
γ-GTP	*γ-glutamyl transpeptidase*
GOT	*Glutamate oxaloacetate transaminase*
GPT	*Glutamate pyruvate transaminase*
IEC	*Independent Ethics Committee*
IRB	*Institutional review board*
LAD	*Left atrial diameter*
LDH	*Lactate dehydrogenase isozyme*
LVDd	*Left ventricular end-diastolic dimension*
LVEF	*Left ventricular ejection fraction*
NA	*Not applicable*
NIS	*Non interventional study*
NYHA	*New York Heart Association*
PT	*Prothrombin*
SAE	*Serious adverse event*
SRSD	*Single Reference Safety Document*
UACR	*Urinary albumin/creatinine ratio*

2. RESPONSIBLE PARTIES

The Japan Good Post marketing Study Practice officer

Principal Investigator(s) of the Protocol

NA

3. AMENDMENTS AND UPDATES

Protocol version identifier	Date	Amendment of plan/others	Amended section	Summary of amendment	Reason
Amended Version 1	01 December 2018	Others	Front page	Added Pfizer Japan Inc.	For description adjustment
Amended Version 1	01 December 2018	Others	9.4.1. Adverse events	Drug discontinuation was changed to drug withdrawal.	For description adjustment
Amended Version 1	01 December 2018	Others	12. NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Addition associated with establishment of Pfizer R&D Japan G.K.	For description adjustment
Amended Version 1	01 December 2018	Others	16.1. Contact information for the contents of the study	Change of description associated with establishment of Pfizer R&D Japan G.K. Addition of e-mail address	For description adjustment
Initial Version	28 March 2017	NA	NA	NA	NA

4. MILESTONES

Milestone	Planned date
Start of data collection	July 2017
End of data collection	June 2020
Final study report	June 2020

5. RATIONALE AND BACKGROUND

Selara® Tablets 25 mg, 50 mg, and 100 mg (generic name: eplerenone) are a selective aldosterone blocker developed by Pfizer. In Japan, these were approved for the indication of "hypertension" on July 31, 2007, and Selara® Tablets 25 mg and 50 mg (hereinafter, this drug) were approved for the indication of "chronic heart failure (CHF)" on December 19, 2016.

The purpose of the Drug Use Investigation of Selara® Tablets (An investigation for CHF) is to confirm the safety of this drug when used in CHF patients, particularly CHF patients with moderate renal impairment, under actual medical practice. Information obtained in this study shall be used to report Ministry of Health, Labour and Welfare (MHLW), Pharmaceuticals and Medical Devices Agency (PMDA) and Pfizer Inc. which is the corporate parent of marketing authorization holder (or sponsor) of this study. It shall be used for application of re-examination (including Japan Periodic Safety Report), re-evaluation, preparation of material for proper use information of this drug, academic articles and activities for information service.

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), "MHLW Ordinance on the Partially Revision of the MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices and on the Partially Revision of the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 26, dated March 11, 2013), and the "Enforcement of the MHLW Ordinance on the Partially Revision of the MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, and Medical Devices, and on the Partially Revision of the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (PFSB Notification No. 0311-7, dated March 11, 2013).

Data obtained from the patients registered in this Study will be reported to the MHLW pursuant to the Pharmaceutical and Medical Device Act; pertinent to which, 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 present 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 any form or shape.

6. RESEARCH QUESTION AND OBJECTIVES

6.1. Safety Specifications

Important Identified Risks:

[redacted]

- Hyperkalaemia
- Events related to hypotension

Important Potential Risks:

- Renal impairment
- Concomitant use of CYP3A4 inhibitor

Important Missing Information:

- Safety in the diabetes patients with micro albuminuria or proteinuria
- Safety in the patients with renal impairment

6.2. Research question and primary objectives

To confirm the safety of this drug when used in CHF patients with moderate renal impairment under actual medical practice.

[Reason for this objective]
Moderate renal impairment was contraindication in the indication of hypertension but not in the indication of CHF. In the domestic phase III study, use experience in Japanese CHF patients with moderate renal impairment was limited.

In the Drug Use Investigation in Japanese hypertension patients, 470 in total 3166 patients with moderate or severer renal impairment received, even though eplerenone was contraindicated in those patients. The incidence rate of treatment-related AEs observed in these 470 patients was higher than that in the other population. Hyperkalaemia was observed at the highest incidence rate in these patients. Treatment-related adverse events observed in more than 3 patients were hyperkalaemia in 8 patients (1.70%), renal impairment in 4 patients (0.85%) and blood potassium increased in 3 patients (0.64%).

For the risk mitigation, following sentences are added in the Dosage and Administration section (for CHF indication) in J-PI: Patients with moderate renal impairment should start with 25 mg every other day and the maximum dosage should be 25 mg once daily ; dose should be reduced or interrupted according to serum potassium level and patient's conditions. In view of this situation, it is important to confirm safety on use in Japanese CHF patients with moderate renal impairment for risk management of this drug. Therefore, drug use investigation for Japanese CHF patients with moderate renal impairment will be conducted.

6.3. Research question and secondary objectives

To confirm the safety of this drug when used in CHF patients under actual medical practice.

To confirm the effectiveness of this drug when used in CHF patients under actual medical practice.

7. RESEARCH METHODS

7.1. Study design

This study is a multi-center cohort study of patients with CHF receiving this drug. The investigators complete the case report form (CRF) based on source documents such as medical records that include data obtained in daily medical practice.

7.2. Setting

Subjects of this study are patients who meet the inclusion criteria and are registered within 14 days including the start date of administration of this drug.

7.2.1. Inclusion criteria

Patients in whom treatment with this drug is for CHF

The Indication, and Dosage and Administration at approval for this drug are as follows. When using this drug, refer to the latest package insert of this drug.

[Indication]
Patients currently receiving angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist, β blocker, diuretic, or other products as a standard treatment of:
Chronic Heart Failure

[Dosage and Administration]
In adults, usually, administer the initial dose of 25 mg once daily, and according to the patient's conditions and serum potassium level, increase dosage up to 50 mg once daily after 4 weeks; patients with moderate renal impairment should start with 25 mg once every other day and the maximum dosage should be 25 mg once daily.

Also, dose should be reduced or interrupted according to serum potassium level and patient's conditions.

[Precautions for Dosage and Administration]
(1) Patients with moderate renal impairment (a creatinine clearance more than 30- less than 50 mL/min) should commence on 25 mg of this drug once every other day and dosage can be increased up to 25 mg once daily after 4 weeks depending on the serum potassium level and patient's condition. The maximum dosage should be 25 mg once daily. [Regarding to the adjustment based on eGFR used in clinical studies, see "Clinical studies"]
(2) Serum potassium should be monitored periodically. Adjust the dosage in accordance with Table 1. [See "Important Precautions"]

Table 1. Adjustment of Dosage and Administration according to Serum Potassium Level

Serum Potassium Level (K+) mEq/L	Adjustment of Dosage and Administration
less than 5.0	In the case of 50 mg once daily: Maintain In the case of 25 mg once daily: Increase to 50 mg once daily In the case of 25 mg every other day: Increase to 25 mg once daily
5.0-5.4	Maintain
5.5-5.9	In the case of 50 mg once daily: Decrease to 25 mg once daily In the case of 25 mg once daily: Decrease to 25 mg every other day In the case of 25 mg every other day: Withhold
not less than 6.0	Withhold

It can be restarted at a dose of 25 mg every other day when K+ has fallen below 5.0 mEq/L.

7.2.2. Exclusion criteria

Patients who were previously registered for this study.

Patients who received this drug within the past three months regardless of the reason for use.

7.2.3. Study sites

Conduct the study at 150 sites including Department of Cardiology, Department of Cardiovascular Medicine, etc.

7.2.4. Planned study period

The planned period covered by this study is as follows.

Investigation period: July 2017 to June 2020

Registration period: July 2017 to June 2018

(Even before the end of the registration period, the registration will be terminated if the target number of subjects is reached.)

7.2.5. Study method

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

7.2.6. Observation period

7.2.6.1. Observation period

One year (52 weeks) from the start date of administration.

However, in patients who discontinue treatment with this drug, the period will be from the start date of administration to the first consultation day after the discontinuation day of treatment with this drug.

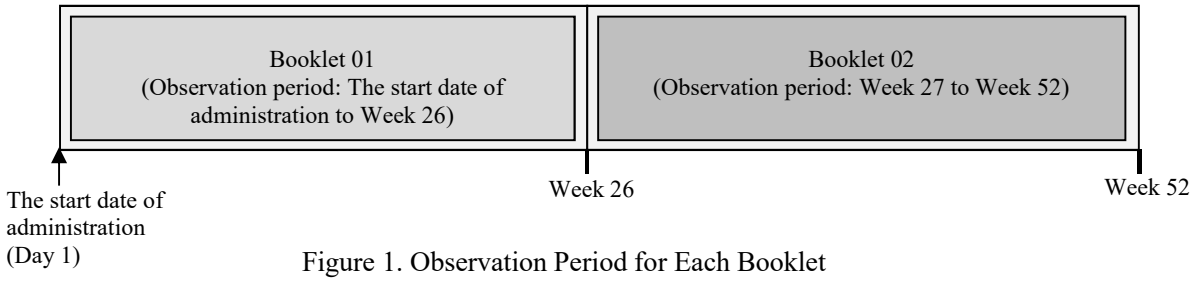

Figure 1. Observation Period for Each Booklet

7.2.6.2. Rationale for observation period

Regarding efficacy, a 1-year observation period was considered to be necessary because the overall mortality, cardiovascular deaths, etc. specified as efficacy endpoints in this study will be compared to the results of other researches/studies for the following reasons.

Based on the data of the domestic epidemiological study CHART-1[1)] (N=1154) and JCARE-CARD[2)] (N=847[a]), the results on all-cause mortality before year one of the assessment period are 7.3% and 8.9% respectively, showing that life prognosis of CHF patients as the target patients of this study is not good.

Regarding the overall mortality and cardiovascular deaths in this study, the number of deaths and death rate (%), death rate (%) after 1 year observation period, death rate based on person-year method (the number of deaths in 100 person-year) will be calculated and compared to the results of the domestic Phase III study or domestic epidemiological studies.

Regarding safety, a 1-year observation period was considered to be long enough to collect and confirm the safety data under daily medical practice sufficiently.

As shown above, the observation period of this study was determined to be 1 year (52 weeks).

a: CHF patients with systolic dysfunction to be able to be followed up

1) Shiba N, Watanabe J, Shinozaki T, et al. Circ J. 2004(5);68:427-34.
2) Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, et al. Circ J. 2009;73(10):1893-900.

7.3. Variables

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

Table 2. Schedule of Observation

Variables	Timing	Registration Form	CRF		
		At the time of registration	Observation period		
			Booklet 01		Booklet 02
			Before administration	Start date of administration to Week 26	Week 27 to Week 52
Patient Background	ID number (other than medical record number)	●			
	Gender	●			
	Age	●			
	Inclusion criteria/Exclusion criteria	●			
	Start date of administration (MMDDYYYY)	●			
	Body weight	●			
	Serum creatinine	●			
	Height		●		
	Hospitalization status (inpatient/outpatient)		●		
	History of hospitalization due to cardiovascular event		●		
	Disease to be investigated (CHF) and disease duration		●		
	NYHA Functional Classification		●		
	Underlying heart disease		●		
	Reason for treatment with this drug		●		
	History of treatment with device therapy		●		
	Presence/absence and severity of hepatic impairment		●		
	Presence/absence and severity of renal impairment		●		
	Disease history		●		
Targeted drug use record			◄———	———	———►
Whether or not treatment with this drug is continued				◄———	———►
History of previous treatment drugs for the targeted disease (in past 3 months) and concomitant drugs			◄———	———	———►
Tests/clinical laboratory tests	Blood pressure/body weight		◄———	———	———►
	Cardiac function test		◄———	———	———►
	Clinical laboratory tests		◄———	———	———►
Clinical evaluation	NYHA Functional Classification			◄———	———►
	Clinical effectiveness (doctor's evaluation)			◄———	———►
Presence/absence of pregnancy (in women only)			◄———	———	———►
Adverse events (any adverse event)				◄———	———►

[redacted]

	Registration Form	CRF		
Variables \ Timing	At the time of registration	Observation period		
		Booklet 01		Booklet 02
		Before administration	Start date of administration to Week 26	Week 27 to Week 52
Survival confirmation			◄———	———►

7.3.1. Patient Background

1. Input the information in the Registration Form at the administration of this drug.
   a. ID number (other than medical record number)
   b. Gender
   c. Age
   d. Setting (inclusion criteria/exclusion criteria)
   e. Start date of administration (MMDDYYYY)
   f. Body weight (kg) (latest measurement result by one month before the administration of treatment)
   g. Serum creatinine (mg/dL) (latest measurement result by one month before the administration of treatment)

2. The following will be recorded in CRF at the administration of this drug.
   a. Height (cm)
   b. Hospitalization status (inpatient/outpatient)
   c. History of hospitalization due to cardiovascular event (before the administration of treatment with this drug)
      (i) Presence/absence of hospitalization due to cardiovascular event
      (ii) Number of times of hospitalization due to cardiovascular event

   Hospitalization due to cardiovascular event is defined as hospitalization due to any of the following:
   - Cardiac failure
   - Myocardial infarction
   - Angina unstable
   - Arrhythmia (Atrial fibrillation, Atrial flutter, Arrhythmia supraventricular, or Ventricular arrhythmia)
   - Stroke or cerebrovascular attack
   - Other causes related to cardiovascular system

   Hospitalization for treatment of a cardiovascular event existing from before the study, excluding those not associated with the development of a new cardiovascular event or with a worsening of the existing cardiovascular disease (e.g., for work-up of persistent lab abnormality observed from before treatment with this drug)

   d. Disease to be investigated (CHF)
      (i) Onset time
   e. Underlying heart disease
      (i) Ischaemic heart disease
      (ii) Non-ischaemic heart disease

f. NYHA Functional Classification (most recent within one month before the administration of treatment with this drug)
(i) Presence/absence of evaluation
(ii) Evaluation result
g. Reason for treatment with this drug
h. History of treatment with device therapy (before the administration of treatment with this drug)
(i) Presence/absence of history of treatment with device therapy
(ii) Details of treatment with device therapy
i. Presence/absence and severity of hepatic impairment: If hepatic impairment is present, classify the severity by reference to the criteria in Table 3.

Table 3. Rough Standards for Determination of Severity of Hepatic Impairment

Severity / Variable	Mild	Moderate	Severe
Total bilirubin (mg/dL)	1.6 to <3.0	3.0 to <10	≥10
GOT, GPT (U)	1.25×N to <2.5×N 50 to <100	2.5×N to <12×N 100 to <500	≥12×N ≥500
Al-P	1.25×N to <2.5×N	2.5×N to <5×N	≥5×N
γ-GTP	≥1.5×N	—	—
LDH	≥1.5×N	—	—
PT	—	—	≤40%
Symptom, etc.	—	Jaundice, Hepatomegaly, Right hypochondrial pain, Hepatic steatosis	Bleeding tendency, Symptoms of hepatic failure such as consciousness disturbed (Hepatitis fulminant), Hepatic cirrhosis, Hepatic tumour, Jaundice persisting for ≥6 months

N: Upper limit of normal for each institution
(Source: PAB/SD Notification No. 80 dated June 29, 1992 “Seriousness Grading Criteria for Adverse Reactions to Pharmaceuticals”)

j. Presence/absence and severity of renal impairment: If renal impairment is present, classify the severity by reference to the criteria in Table 4.

Table 4. Rough Standards for Determination of Severity of Renal Impairment

Severity / Variable	Mild	Moderate	Severe
BUN (mg/dL)	Higher than 1×N to <25	25 to <40	≥40
Creatinine (mg/dL)	Higher than 1×N to <2	2 to <4	≥4
Urine protein	1+	2+ to 3+	Higher than 3+
Haematuria	Microscopic	Macroscopic	Macroscopic, Clotting blood
Urine output	—	≤500 mL/24 hr or oliguria/polyuria*	≤100 mL/24 hr or anuria
Serum potassium level (mEq /L)	—	5.0 to <5.5	≥5.5
Other symptom, etc.	—	—	Nephrotic syndrome, Acute renal failure (interstitial nephritis, tubulonecrosis, renal necrosis, renal papillary necrosis, renal cortical necrosis), Chronic renal failure (interstitial nephritis, tubulonecrosis, renal necrosis, renal papillary necrosis, renal cortical necrosis), Uraemia, Hydronephrosis

N: Upper limit of normal for each institution
Note)* Polyuria: It refers to renal diabetes insipidus.
(Source: PAB/SD Notification No. 80 dated June 29, 1992 “Seriousness Grading Criteria for Adverse Reactions to Pharmaceuticals”)

Important: Hepatic impairment/renal impairment refer to an event requiring follow-up observation to which clinical attention should be paid, not transient lab abnormality.

k. Presence/absence of pregnancy
l. Disease history: Enter the presence/absence of relevant diseases and syndromes. Enter “Previous” if a disease was healed before the administration of this drug and enter “Current” if a disease has developed at the administration of this drug. If the disease history includes diabetes mellitus, enter whether or not diabetes mellitus is associated with micro albuminuria (UACR ≥30) or proteinuria (not including false positive (±)).However, if it has developed or occurred after the start date of administration of this drug, enter its details in the section of adverse events.

7.3.2. Administration record of targeted drug

Enter the daily dose level of this drug administered from the start date of administration to the last day of the observation period, as well as the treatment period. If the daily dose is changed or this drug is ceased, also enter the reason for dose change/cessation of this drug.

1. Daily dose
2. Treatment period
3. Reason for dose change/cessation of this drug

7.3.3. Whether or not treatment with this drug is continued

1. Whether or not treatment with this drug is continued
2. First consultation day after the discontinuation day of treatment with this drug
3. Reason for discontinuation of treatment with this drug

If treatment with this drug is not continued until the last day of the observation period in this study, select and enter the reason for it from among the following. If any adverse event is selected, enter its details in the section of adverse events. If other is selected, enter the reason for it as well.

1. Insufficient clinical effectiveness
2. Adverse event
3. No re-visit [a)]
4. Other [b)]

a. Enter it only in Booklet 02.
b. If "Other," enter the reason for it; for example, the patient's will unrelated to the adverse event.

7.3.4. Previous treatment drugs and concomitant drugs

7.3.4.1. Treatment drugs for chronic heart failure/hypertension; Contraindicated concomitant drugs; Concomitant drugs requiring caution (Collect information for all subjects)

Select the presence/absence of treatment with drugs falling under "7.3.4.1.1. Relevant drugs" from among drugs used between three months before the start date of administration and the last day of the observation period.

If "Yes" is selected as the presence of treatment in the above section, enter the name of the drug(s) administered in the section of "Nonproprietary name or product name" and then enter the treatment period, etc.

It is not necessary to enter drugs other than those under any of the following categories.

7.3.4.1.1. Relevant drugs

- Diuretics (excluding potassium-conserving diuretics)
- Potassium-conserving diuretic (*contraindication for concomitant use) [a)]
- Angiotensin-converting enzyme (ACE) inhibitors [b)]
- Angiotensin II receptor blockers (ARB) [b)]
- β blockers
- Ca antagonists
- Other antihypertensive drugs (α blockers, direct renin inhibitors, etc.)
- Digitalis preparations
- Antiarrhythmic drugs
- Antiplatelet drugs
- Oral anticoagulant drugs
- Statin drugs
- Itraconazole (*contraindication for concomitant use) [c)]
- Ritonavir (*contraindication for concomitant use) [c)]
- Nelfinavir (*contraindication for concomitant use) [c)]
- Other CYP3A4 inhibitors [b)]
- Aliskiren [b), d)]
- Cyclosporin [b)]
- Tacrolimus [b)]
- Drospirenone [b)]
- Nonsteroidal anti-inflammatory drugs (NSAIDs) [e)]
- Potassium preparations [b)]

a. Contraindicated concomitant drugs (When they are used concomitantly, the potassium-retaining action may be potentiated, thereby possibly elevating the serum potassium level)
b. Concomitant drugs requiring caution (When they are used concomitantly, the potassium-retaining action may be potentiated, thereby possibly elevating the serum potassium level)

c. Contraindicated concomitant drugs (Potent CYP3A4 inhibitors inhibit the metabolism of this drug, and consequently the plasma concentration of this drug may be elevated, thereby possibly inducing an elevation in the serum potassium level)
d. Describe in the section of other antihypertensive drugs (α blockers, direct renin inhibitors, etc.).
e. Concomitant drugs requiring caution (Clear mechanisms are unknown, but when the production of prostaglandin is suppressed, the sodium-retaining action may diminish the antihypertensive action, and the potassium-retaining action may elevate the serum potassium level. The occurrence of severe hyperkalaemia was reported in patients with renal impairment when they were used concomitantly.)

7.3.4.2. Other previous treatment drugs and concomitant drugs (Collect information for subjects who have any adverse event corresponding to "renal impairment")

If any adverse event corresponding to "renal impairment" is observed, select the presence/absence of treatment with drugs other than this drug and "7.3.4.1.1. Relevant drugs" from among drugs used between three months before the start date of administration and the last day of the observation period.

If "Yes" is selected as the presence of treatment in the above section, enter the name of the drug(s) administered in the section of "Nonproprietary name or product name" and then enter the treatment period.

7.3.5. Tests/clinical laboratory tests

Enter whether or not tests are implemented and test results for the clinical course from before administration of this drug to the last day of the observation period. Before administration of this drug, enter the latest test results for tests implemented during the period from three months before the start of administration to immediately before the start of administration (including the start date of administration) (For cardiac function tests: from six months before the start of administration). At the end of the observation period, enter the test results within one month after the last day of the observation period. If there are no test results for appropriate dates, enter the test results for the day of tests closest to the last day of the observation period. For any test results, enter the implementation date and test results. Regarding clinically-problematic abnormal changes in test values compared to the values before the start of administraiton, enter the details in the section of adverse events as well.

7.3.5.1. Blood pressure/body weight

Blood pressure systolic, blood pressure diastolic, and body weight

7.3.5.2. Cardiac function test

Left ventricular ejection fraction (LVEF), left ventricular end-diastolic dimension (LVDd), and left atrial diameter (LAD) confirmed by echocardiography

7.3.5.3. Clinical laboratory tests

Serum creatinine, serum potassium, BUN, plasma BNP, and serum NT-proBNP

7.3.6. Clinical evaluation

Enter the evaluation result obtained by using the following evaluation scale for clinical evaluation.

7.3.6.1. NYHA Functional Classification

For clinical evaluation, enter whether or not evaluation based on NYHA Functional Classification is done and the evaluation result. The evaluation result to be entered should be the one obtained on the last day of the observation period. If treatment with this drug is discontinued, enter the result of evaluation implemented on the last day of observation. However, if no evaluation is done in the relevant period, enter the evaluation result obtained in the period closest to the relevant period.

(1) Whether or not evaluation based on the NYHA Functional Classification is done
(2) Date of evaluation based on the NYHA Functional Classification

(3) Results of evaluation based on the NYHA Functional Classification

Reference) NYHA Functional Classification

Class I: Having a heart disease, but with no limitation of physical activity. Ordinary physical activity does not cause marked fatigue, palpitations, dyspnoea, or anginal pain.

Class II: Having a mild limitation of physical activity. No symptom at rest. Ordinary physical activity causes fatigue, palpitations, dyspnoea, or anginal pain.

Class III: Having a severe limitation of physical activity. No symptom at rest. Exertion less than ordinary activity causes fatigue, palpitations, dyspnoea, or anginal pain.

Class IV: Any physical activity is limited due to a heart disease. A symptom of heart failure or anginal pain is present even at rest. These symptoms can be exacerbated by slight exertion.

(Source: Igaku Shoin's Medical Dictionary 2nd Edition, issued on February 15, 2009)

7.3.6.2. Clinical effectiveness (investigator's evaluation)

The investigator will evaluate this drug based on the following items for judging the clinical effectiveness on the last day of the observation period as compared to the status before the administration of this drug (including the start date of administration), and enter the evaluation date and its results. If treatment with this drug is discontinued, enter the result of evaluation implemented on the last day of observation. However, if there is no result for the relevant period, enter the result obtained in the period closest to the relevant period.

Clinical effectiveness
(1) Yes
(2) No
(3) Unavailable (In this case, the reason should be recorded.)

7.3.7. Presence/absence of pregnancy (in women only)

Enter the presence/absence of pregnancy between the start date of administration and the last day of the observation period.

7.3.8. Adverse events

Regardless of causal relationship with this drug, the following information related to all adverse events that occur between the start of administration and the last day of the observation period (the last day of observation if treatment is discontinued) should be entered in the section of adverse events. Conduct a detailed investigation separately if the sponsor judges it necessary.

- Presence/absence of adverse event
- Name of adverse event
- Category of adverse event
  Also enter whether the entered adverse event is an "event related to hypotension" or an "event related to hyperkalaemia."
- Date of occurrence
- Procedure ([1] Change of treatment with this drug; [2] Additional treatment for the adverse event)
- Seriousness
- Whether or not the event(s) has led to death; Whether or not the event(s) has led to hospitalization
  If the event has led to death, enter information on whether or not it is "cardiovascular death," or if the event has led to hospitalization, enter information on whether or not it is "hospitalization due to a cardiovascular event."
- Outcome of the adverse event to present; Outcome date

- Causal relationship with this drug

If there is any adverse event related to abnormal changes in test values from clinical laboratory tests and physiological function tests, etc., enter the following information in the section of tests related to adverse events.

- Laboratory parameter
- Site reference value
- Unit
- Test date
- Results

Cardiovascular deaths are defined as deaths due to any of the following causes:

- Cardiac failure
- Myocardial infarction
- Arrhythmia (Atrial fibrillation, Atrial flutter, Arrhythmia supraventricular, or Ventricular arrhythmia)
- Stroke or cerebrovascular attack
- Other causes related to cardiovascular system

If any adverse event corresponding to “renal impairment” is observed, enter information on drugs other than this drug and “7.3.4.1.1. Relevant drugs” (Refer to the section “7.3.4.2. Other previous treatment drugs and concomitant drugs [collect information for subjects who have any adverse event corresponding to “renal impairment”]).

Note: Adverse events are any and all unfavorable events (including clinically significant abnormal changes in laboratory tests) occurring in patients after starting treatment with this drug regardless of their causal relationship. Serious adverse events 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.

7.3.9. Survival confirmation

Regarding the status from the start of administration to Week 52, enter the following information in the section of survival confirmation.

- Last date of survival confirmation
- Result of survival confirmation

7.3.10. Major investigation items

7.3.10.1. Hyperkalaemia

Due to the mechanisms of action of this drug, a risk of hyperkalaemia is expected. It was observed as an adverse reaction in clinical studies by the time of approval. It is also known as a clinically-significant adverse reaction to similar drugs, and may become severe at the time of onset, thereby possibly threatening the life, and as such, it is specified as an important identified risk. For this event specified as a major investigation item, information on the onset date of the adverse event, procedure (change of treatment with this drug; additional treatment for the adverse event), seriousness, outcome, causal relationship with this drug, and factors for the adverse event other than this drug will be collected, and risk factors and onset time will be investigated.

7.3.10.2. Events related to hypotension

Due to the mechanisms of action of this drug, the possibility that adverse events related to hypotension may occur cannot be ruled out, and associated secondary events (fall, loss of consciousness, etc.) may occur, possibly leading to clinically-significant events, and therefore these events are specified as important identified risks. For this event specified as a major investigation item, information on the onset date of the adverse event, procedure (change of treatment with this drug; additional treatment for

the adverse event), seriousness, outcome, causal relationship with this drug, and factors for the adverse event other than this drug will be collected, and risk factors and onset time will be investigated.

7.4. Data sources

In this study, the investigators extract the necessary information from source documents such as medical records in accordance with the protocol.

7.5. Sample size

7.5.1. Planned sample size

A total of 1000 CHF patients as subjects included in the safety analysis set (including at least 300 patients with moderate renal impairment)

7.5.2. Rationale for sample size

Table 5 shows the number and proportion of cases of adverse events related to hyperkalaemia and renal impairment that occurred within 52 weeks (364 days) after the start of administration, for which a causal relationship could not be ruled out, in all CHF patients and patients with moderate renal impairment in the domestic Phase III study (Study A6141114) and the foreign Phase III study (Study EMPHASIS-HF).

Table 5. Adverse Events related to Hyperkalaemia and Renal Impairment that Occurred within 52 Weeks (364 Days) after the Start of Administration in Eplerenone Group for which Causal Relationship Could Not Be Ruled Out - Safety Analysis Set

Preferred Term	Patients with moderate renal impairment eGFR < 50 mL/min/1.73m^2	All CHF patients
Study A6141114	N=37	N=111
Hyperkalaemia	2 (5.4)	3 (2.7)
Chronic kidney disease	0	1 (0.9)
Renal impairment	1 (2.7)	1 (0.9)
Study EMPHASIS-HF	N=224 [a]	N=1360
Hyperkalaemia	20 (8.9)	56 (4.1)
Renal failure	1 (0.4)	4 (0.3)
Renal impairment	6 (2.7)	12 (0.9)

n (%)
[a]: Including two patients with eGFR <30 mL/min/1.73m^2.

In Study A6141114, the ratio of patients with moderate renal impairment to all CHF patients in Japanese was 34.4% (76/221). Taking into account this result and the results of a Japanese epidemiological survey[3)], the ratio of patients with moderate renal impairment to CHF patients in Japan is estimated to be approximately 30%. Given that the target sample size of all CHF patients is 1000 patients, the number of patients with moderate renal impairment is expected to be approximately 300-350.

As shown in Table 5, the incidence rate of adverse events related to renal impairment for which a causal relationship could not be ruled out was 3.1% (8/261) in patients with moderate renal impairment in the combined results from Study A6141114 and Study EMPHASIS-HF conducted in CHF patients with systolic dysfunction in which the same primary endpoint (cardiovascular deaths or hospitalization due to heart failure) was compared to a placebo treatment group. Assuming that 3.1% is the true incidence rate of adverse events related to renal impairment for which a causal relationship cannot be ruled out in patients with moderate renal impairment, the expected number of cases of adverse events related to

renal impairment for which a causal relationship cannot be ruled out is 9.3-10.9 when collecting 300-350 patients with moderate renal impairment.

Also, assuming that 8.4% (22/261) is the true incidence rate of adverse events related to hyperkalaemia for which a causal relationship cannot be ruled out in patients with moderate renal impairment, similarly to the above-mentioned method, the expected number of cases of adverse events related to hyperkalaemia for which a causal relationship cannot be ruled out is 25.2-29.4.

If events which true incidence rate is 3.1% and 8.4% are observed in 300 patients, the estimated incidence rate will be 1.1%-5.1% and 5.3%-11.5%, respectively, with a probability of approximately 95%.

Assuming that the true incidence rate of adverse events related to renal impairment and hyperkalaemia in all CHF patients for which a causal relationship cannot be ruled out is 1.2% (18/1471) and 4.0% (59/1471), respectively, the expected number of cases of adverse events for which a causal relationship cannot be ruled out is 12.0 and 40.0, respectively, when collecting 1000 CHF patients. Events can be observed in approximately 6-19 patients and 28-53 patients, respectively, with a probability of approximately 95%.

If events which true incidence rate is 1.2% and 4.0% are observed in 1000 patients, the estimated incidence rate will be 0.5%-1.9% and 2.8%-5.2%, respectively, with a probability of approximately 95%.

As described above, regarding adverse events related to hyperkalaemia and renal impairment for which a causal relationship cannot be ruled out, a target sample size of 1000 patients may enable evaluation of the safety profile between clinical studies and use-results surveys in terms of patient background including the presence/absence of comorbid moderate renal impairment as well as seriousness, outcome, etc. of adverse events.

3) Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, et al. Circ J 2009;73:1442.

7.6. Data management

7.6.1. Data collection method

The data for this study will be entered in CRFs and confirmed using an electronic post-marketing data collection system for drugs (Electronic Data Capture or EDC, hereinafter referred to as this system) provided by the sponsor on the Internet.

7.6.2. Patient registration

The investigator will enter registration items on the patient registration screen of this system. Patient registration will be performed within 14 days including the start date of administration.

7.6.3. Point of consider for completion, revision, and submission of CRF

7.6.3.1. Data entry

The investigator shall, upon confirming the study items, enter the data in this system based on source documents such as medical records.

7.6.3.2. Data revision

Upon receiving Sponsor's inquiry on the entered contents of the CRF (query forms), the investigator will again confirm the information of source documents such as medical records described earlier, and as required, correct relevant contents.

7.6.3.3. Submission

After completion of all entries and revisions of study items, the investigator will again confirm the entered contents of the CRF and re-investigation, and affix his or her electronic signature.

7.7. Data analyses

1) Definition of analysis sets
The safety analysis set (SAS) is defined as patients in whom treatment with this drug was confirmed.
The efficacy analysis set is defined as patients in whom treatment with this drug was confirmed and the efficacy could be evaluated in CHF patients.

2) Method of Analysis
(1) Safety analysis
Events for which a causal relationship with this drug cannot be ruled out will be handled as adverse reactions, and the number and proportion of cases of adverse reactions will be aggregated by System Organ Class and Preferred Term.

For patients with renal impairment, moderate renal impairment, or hepatic impairment, elderly patients (≥65 years, ≥75 years), pediatric patients (<15 years), and diabetes patients with micro albuminuria or proteinuria, the safety will be comparatively investigated versus other populations.

In addition, the occurrence status of adverse reactions related to hyperkalaemia, renal impairment, or blood pressure decreased will be investigated in terms of risk factors and onset time.

(2) Efficacy analysis
Regarding each evaluation item for clinical evaluation, the number and proportion of cases will be aggregated by level from the results. Regarding the overall mortality and cardiovascular deaths in the study, the number of deaths and death rate (%), death rate (%) after 1 year observation period, death rate based on person-year method (the number of deaths in 100 person-year) will be calculated. For reference, the results will be compared to the domestic Phase III study or Japanese epidemiological surveys (CHART-1, CHART-2, JCARE-CARD, etc.). These comparisons will be performed with adjustment of factors such as patient background that are considered available or appropriate at the time of evaluation or setting of appropriate subgroups. [a)]

a. For the domestic Phase III study, comparisons to death rates adjusted for age, gender, and NYHA Functional Classification by using individual data such as patient background collected in the study will be considered; and for the Japanese epidemiological surveys, comparisons to death rates adjusted for gender and NYHA Functional Classification by using aggregate data such as patient background from published papers, etc. will be considered.

Detailed methodology for statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be stored by Pfizer. The SAP may modify the plans outlined in the Study Protocol; any major modifications of primary endpoint definitions or their analyses will be also reflected in amendment of the Protocol.

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 records.

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 limitation to the judgment on whether or not a risk of developing adverse events and adverse reactions increases due to the administration of the targeted 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 records, the set data may not be collected or there may be missing information.

7.10. Other aspects

NA

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient information and consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

In this study, the information will be collected by transcribing medical record information described in routine medical practice. In doing so, the informed consent will not be used because the information collected from medical records is anonymized and does not contain any information that identifies individual patients.

8.2. Patient withdrawal

NA

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

In this study, the review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) is not essential.

8.4. Ethical conduct of the study

This study is excluded from the subject since it is included in the scope of application of the “Good Post-Marketing Study Practice” (Ordinance of Ministry of Health, Labour and Welfare No. 171 of December 20, 2004).

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

For an event that needs to be reported by the investigator within 24 hours, the site staff will request the investigator to report it at the start of the study and regularly visit the investigator during the investigation period to request the investigator to report it.

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”).”

9.1. Requirements

The table below summarizes the requirements for recording safety events in the CRF and for reporting safety events by the NIS AE 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 breastfeeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section “Definitions of safety events.”

Safety event	Recorded on the data collection tool (e.g. CRF)	Reported on the NIS AE 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 breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

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 a drug under study. 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 time frame. 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 in the data collection tool (e.g. 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 events 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.

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 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 in the data collection tool (e.g. CRF) and the NIS AE 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.

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/aggravation 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 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 sponsor.

Merely repeating an abnormal test result, 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

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

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

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

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

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

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to other department or 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 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 medical examination)
- Optional admission not associated with a sudden change in clinical condition (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 tests or procedures required by the study protocol)

9.4.3. 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:

A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) this drug, or a 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).

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).

As a general rule, prospective and retrospective EDP reports 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 this drug, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AE Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to this drug in a pregnant woman (e.g., a subject reports that she is pregnant and has been accidentally exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AE 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 is 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 is as 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 accordance 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 preventable event 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 of medication error.

Overdose, Misuse, Extravasation

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

Lack of efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an 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 Japan Inc. 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 based on the SRSD.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study 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 this 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 the Protocol that the investigator becomes aware of.

11. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION

The organizational system in this study is equivalent to that in Appendix “Organizational System for Post-marketing Study.” The Supervisor for PMS Plan & Operation will be responsible for post-marketing study.

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

Address: 3-22-7 Yoyogi, Shibuya-ku, Tokyo
Company name: Pfizer R&D Japan G.K.
Scope of the outsourced operations: Planning of the study and drafting of the plan, and operations related to study administration, etc.

Address: Sumitomo Fudosan Korakuen Bldg. 9th Floor, 1-4-1 Koishikawa, Bunkyo-ku, Tokyo
Company name: A2 Healthcare Corp.
Scope of the outsourced operations: Operations excluding the management operations of the post-marketing survey, etc. among the study operations such as the registration reception, establishment of post-marketing study data collection system (EDC), and data management

Address: JP Tower 29th Floor, 2-7-2 Marunouchi, Chiyoda-ku, Tokyo
Company name: Medidata Solutions, Inc.
Scope of the outsourced operations: Operations related to establishment and operation of post-marketing study data collection system (EDC), etc.

Address: Acropolis TOKYO Bldg., 6-29 Shinogawamachi, Shinjuku-ku, Tokyo
Company name: EPS Corporation
Scope of the outsourced operations: Aggregation/analysis operations

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

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

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

2) Review the necessity for changing the contents of this study plan including the presence or absence of new safety specifications (continuation of the study, implementation of additional study, etc.).

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

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

Investigate and report the safety at the time of submission of Periodic Safety Reports, at the time of completion of the registration (at the time of preparation of the 3rd or 4th Periodic Safety Report), and at the time of completion of the study (at the time of preparation of the 6th Periodic Safety Report). Report the number and ratio of patients with moderate renal impairment to all registered subjects at the time of completion of the registration (at the time of preparation of the 3rd or 4th Periodic Safety Report). Also, report the overall results of the study and the discussion of the results at the time of completion of the study (at the time of preparation of the 6th Periodic Safety Report).

15. OTHER ASPECTS

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 Study Protocol will be amended if necessary. Also, the need for amendment of the Protocol will be examined and will be amended as necessary 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 if any problem or question is observed

In the cases where the onset of 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 efficacy and safety of the drug compared to those prior to the approval, the onset of a different kind of adverse reaction is suggested, etc., the amendment of the package insert and implementation of a new special use-results survey or post-marketing clinical study should be considered.

CCI

[redacted]

17. REFERENCES

NA

18. LIST OF TABLES

19. LIST OF FIGURES

LIST OF STAND ALONE DOCUMENTS

NA

ADDITIONAL INFORMATION

NA

[redacted]

CCI

[redacted]