DRUG USE INVESTIGATION OF EFFEXOR® SR CAPSULES

STUDY PROTOCOL

Pfizer Japan Inc.

.

[redacted]

Study information

Title	DRUG USE INVESTIGATION OF EFFEXOR® SR CAPSULES
Protocol ID	B2411278
Protocol version identifier	Amended Version 2
Date of last version of protocol	6 January 2016
Active substance	Venlafaxine Hydrochloride
Medicinal product	Effexor® SR Capsules 37.5 mg/Effexor® SR Capsules 75 mg
Research question and objectives	To confirm the safety and efficacy of Effexor under actual medical practice
Author of the protocol	PPD PMS Planning & Operation Group 1 Post Marketing Study Strategy and Management

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	*Adverse event*
ALT	*Alanine transaminase*
Al-P	*Alkaline phosphatase*
AST	*Aspartate transaminase*
BUN	*Blood urea nitrogen*
CGI	*Clinical Global Impressions*
CGI-I	*Clinical Global Impressions-Improvement*
CGI-S	*Clinical Global Impressions-Severity*
CPK	*Creatine phosphokinase*
EM	*Extensive metabolizer*
γ-GTP	*γ-glutamyl transpeptidase*
GGT	*γ-glutamyl transpeptidase*
GOT	*Glutamate oxaloacetate transaminase*
GPT	*Glutamate pyruvate transaminase*
HAM-D	*Hamilton Rating Scale for Depression*
HbA1c	*Hemoglobin A1c*
HDL	*High-density lipoprotein*
IDS-C	*Inventory of Depressive Symptomatology-Clinician Rating*
IM	*Inter mediate metabolizer*
IRB	*Institutional review board*
LDH	*Lactate dehydrogenase isozyme*
LDL	*Low-density lipoprotein*
IEC	*Independent Ethics Committee*
MADRS	*Montgomery - Asberg Depression Rating Scale(MADRS)*
N/A	*Not applicable*
NIS	*Non interventional study*
PHQ	*Patient Health Questionnaire*
PM	*Poor metabolizer*
QIDS-SR	*Quick Inventory of Depressive Symptomatology-Self Report*
SAE	*Serious adverse event*
SIGMA	*Structured Interview Guide for MADRS*
SRSD	*Single Reference Safety Document*
TG	*Triglyceride*
UM	*Ultra-rapid metabolizer*
USPI	*United States package insert*

2. RESPONSIBLE PARTIES

The Japan Good Post Marketing Study Practice Officer

Principal Investigator(s) of the Protocol

N/A

3. AMENDMENTS AND UPDATES

Amendment number	Date	Amendment of the plan/Others	Amended section	Summary of amendment(s)	Reason
Amended Version 2	2018/12/1	Others	9.4. Definitions of safety events	Change in description associated with the revision of 9.4.1. Adverse events	For description adjustment
Amended Version 2	2018/12/1	Others	9.4.1. Adverse events	Change in description from "Drug discontinuation" to "Drug withdrawal"	For description adjustment
Amended Version 2	2018/12/1	Others	12. NAME, ADDRESS AND OUTSOURCED OPERATIONS OF THE PERSON WHO WAS CONTRACTED WITH THE OPERATIONS	Addition associated with the establishment of Pfizer R&D Japan G.K.	For description adjustment
Amended Version 2	2018/12/1	Others	16.1 Contact information for the contents of the study	Revision associated with the establishment of Pfizer R&D Japan G.K.	For description adjustment
Amended Version 1	2016/1/6	Others	7.2. Setting	Change in description associated with the revision of 7.2.2. Exclusion criteria	For description adjustment
Amended Version 1	2016/1/6	Revision of the plan	7.2.1. Inclusion criteria	It was specified that patients with no prior exposure to this product will be included in this study.	For the revision of the plan
Amended Version 1	2016/1/6	Revision of the plan	7.2.2. Exclusion criteria	Exclusion criteria were reviewed because it is not appropriate to set exclusion criteria in drug use investigations.	For the revision of the plan
Amended Version 1	2016/1/6	Revision of the plan	7.2.3. Study sites	Main departments for the conduct of this study were reviewed, and neurology was	For the revision of the plan

				deleted.	
Amended Version 1	2016/1/6	Others	7.3. Variables	Addition associated with the revision of 7.2.1. Inclusion criteria	For description adjustment
Amended Version 1	2016/1/6	Others	7.3.1. Patient Background 1)	Addition associated with the revision of 7.2.1. Inclusion criteria	For description adjustment
Amended Version 1	2016/1/6	Others	7.3.1. Patient Background Reference) Rough guide for determination on the severity of renal impairment	Test item The description "Symptom, etc." was changed to "Other symptom, etc."	For the modification of a clerical error
Amended Version 1	2016/1/6	Others	7.3.8.1. HAM-D	The source of the assessment results items of the investigation form was specified in a separate section.	For description adjustment
Amended Version 1	2016/1/6	Others	7.3.8.2. MADRS	The source of the assessment results items of the investigation form was specified in a separate section.	For description adjustment
Amended Version 1	2016/1/6	Others	7.3.9.2. Overall improvement (CGI-I)	A direction that the reason for "unevaluable" should be entered if the assessment cannot be made was added.	For description adjustment
Amended Version 1	2016/1/6	Others	7.5.1. Planned sample size	"3 months" was changed to "12 weeks."	For description adjustment
Amended Version 1	2016/1/6	Others	7.5.2. Rationale for sample size	"3 months" was changed to "12 weeks."	For description adjustment
Amended Version 1	2016/1/6	Others	21. ADDITIONAL INFORMATION	The sources of the assessment results items of the investigation form were transferred to this section.	For description adjustment
Initial protocol	2015/10/21	N/A	N/A	N/A	N/A

4. MILESTONES

Milestone	Planned date
Start of data collection	April 2016
End of data collection	March 2020
Final study report	December 2020

5. RATIONALE AND BACKGROUND

Effexor® SR Capsules 37.5 mg and 75 mg (Generic name: Venlafaxine Hydrochloride) (hereinafter referred to as this product) is a sustained-release preparation of venlafaxine hydrochloride (1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexanol-HCl) and antidepressant which is classified into a serotonin-noradrenaline reuptake inhibitor (SNRI). In Japan, the application for approval of marketing authorization was filed in December 2014 for the indication of "depression and depressive state."

The "Drug Use Investigation of Effexor® SR Capsules" will be conducted to collect the safety and efficacy information of this product. The information to be collected in this study will be used to prepare and provide the materials for proper use information of this product.

The study will be conducted based on the "Ministerial Ordinance on Good Post-marketing Study Practice for Drugs" (MHLW Ordinance No. 171 dated December 20, 2004). The case data to be collected in this study will be also reported to the Ministry of Health, Labour and Welfare (MHLW) based on the Pharmaceutical and Medical Device Act.

In this case, the information such as drug name, name of adverse reaction, gender, and age (generation) for applicable case data may be made public as a list of cases on "Pharmaceuticals and Medical Devices Safety Information" and "Supply of Information on Drugs and Medical Devices Website (http://www.info.pmda.go.jp)" by the MHLW.

Furthermore, the collected case data will be also disclosed if any request to disclose the information is made to the MHLW based on the "Act on Access to Information Held by Administrative Organs" (Act No. 42 of May 14, 1999). However, the information on doctor's name and site name will be neither subject to reporting nor posted or disclosed in either case.

6. RESEARCH QUESTION AND OBJECTIVES

To confirm the safety and effectiveness of Effexor under actual medical practice.

6.1. Safety specifications

Serotonin syndrome, Convulsion, Withdrawal syndrome, Increased blood pressure/Hypertensive crisis/Increased heart rate, QT prolongation/Torsade de Pointes (TdP), Lipid effects, Hyponatremia/Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), Stevens-Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)/Erythema multiforme, Anaphylaxis, Urinary retention, Suicidal ideation/Suicide attempt, Mania/Hypomania, Abnormal Bleeding: ecchymoses, hematomas, epistaxis, and petechiae leading to life-threatening hemorrhage, Hostility/Aggression, Ischaemic heart disease, Agranulocytosis/Aplastic anaemia/Pancytopenia/Neutrophil count decreased/Platelet count decreased, Interstitial lung disease (ILD), Noradrenaline effect potentiation by increase in dosage (Insomnia, Blood pressure increased, etc.), Safety in the patient with mild or moderate hepatic impairment, Safety in the patient with mild or moderate renal impairment.

6.2. Other safety investigation item

Safety in adverse events of central nervous system, adverse events of gastrointestinal system, sexual dysfunction, and highly accumulated sites (Liver, Urinary organ, Lung, Eye, and Skin); safety of CYP2D6 by UM/EM/PM/IM; effect on weight.

7. RESEARCH METHODS

7.1. Study design

This is a multi-center open-label study to be conducted in patients who received this product and the case report forms will be filled out based on the medical charts which contain the data obtained from usual daily medical practice.

7.2. Setting

The patients who meet the inclusion criteria and who were registered to this study within 14 days including the start date of treatment with this product will be included in this study.

7.2.1. Inclusion criteria

Patients with no prior exposure to this product who will be administered this product for the first time

The indication and dosage and administration of this product at the time of approval are as follows. Refer to the latest package insert when administering this product.

[INDICATIONS]
Depression/depressive state
[Precautions related to Indications]
1. It is reported that the risks of suicidal ideation and suicide attempt are increased in patients aged 24 and younger receiving antidepressants. In addition, it is suggested that the risks of suicidal ideation and suicide attempt due to the use of venlafaxine may be higher compared to placebo, particularly in patients with major depressive disorder (MDD) aged under 18 years. Therefore, if this drug is used in such patients, the risk-benefit balance should be considered. (Refer to the sections "Pediatric Use" and "Other Precautions.")
2. It has been reported that efficacy has not been established in placebo-controlled trials conducted overseas with MDD patients 7-17 years of age. The appropriateness of this drug for MDD patients under 18 years of age should be carefully considered prior to administration. (Refer to the section "Pediatric Use.")

[DOSAGE AND ADMINISTRATION]
The usual adult starting dosage for oral use is 37.5 mg of venlafaxine once daily, which is increased to 75 mg once daily after a meal from 1 week later. The dose may be adjusted within a range up to 225 mg/day according to the patient's age and symptoms. However, the dose should be increased by 75 mg/day at intervals of not less than 1 week.

[Precautions related to Dosage and Administration]
1. The dosage of Effexor SR should be adjusted to the necessary minimum for each patient while closely observing the patient's condition. (Effects of noradrenaline such as insomnia and increased blood pressure may occur as a result of increased dosage. Refer to the section "Other Precautions.")
2. In patients with moderate hepatic impairment (Child-Pugh class B), the blood concentration may increase, and adverse reactions may be likely to occur, especially in early stage of treatment. Therefore, starting dose of venlafaxine should be 37.5 mg once every 2 days, and after 1 week, increased to 37.5 mg once daily. The dose should be escalated by 37.5 mg/day, in accordance with the patient's condition, within a range up to 112.5 mg/day, at intervals of 1 week or more, while sufficiently monitoring the patient's condition. (Refer to the sections "Careful Administration," "Adverse Reactions" and "PHARMACOKINETICS.")
3. In patients with mild hepatic impairment (Child-Pugh class A), the blood concentration may increase, and adverse reactions may be likely to occur, especially in early stage of treatment. Therefore, dose reduction or prolongation of dosing intervals should be considered as needed, and the patient's condition should be sufficiently monitored when escalating the dose. (Refer to the sections "Careful Administration," "Adverse Reactions" and "PHARMACOKINETICS.")

7.2.2. Exclusion criteria

Exclusion criteria are not provided in this study.

7.2.3. Study sites

The study will be conducted at 150 to 200 sites including the departments of psychiatry, psychosomatic medicine, internal medicine, and neurological science.

7.2.4. Planned study period

This planned period covered by this study is as follows.

Investigation period: April 2016 to March 2020

Registration period: April 2016 to March 2019

(The registration will be completed if a target sample size has been reached even prior to completion of the registration period)

7.2.5. Study method

This study will be conducted under the central registration system until the number of subjects who meet the conditions for registration reaches the number of contract subjects.

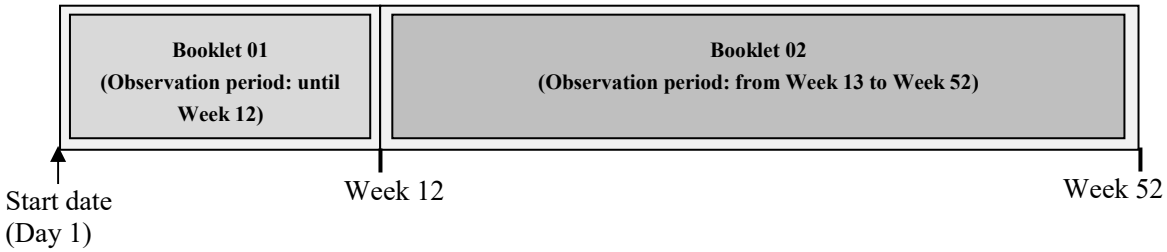
7.2.6. Observation period

Twelve weeks from the start date. The patients who completed the 12-week treatment with this product will be observed up until Week 52.

This study will be conducted using the separate-type case report forms. The results of observation during the following observation periods will be entered to each case report form. However, the information from the date of last treatment until 28 days later will be collected for patients who discontinued this product.

Figure 1. Observation period for Each Booklet

Name of case report form	Observation period
Booklet 01	From the start date until Week 12
Booklet 02	From Week 13 after the start of treatment with this product until Week 52



[redacted]

7.3. Variables

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

Table 1. Schedule of observation

		Registration form	Case report forms		
Variables \ Timing		At registration	Observation period		
			Booklet 01		Booklet 02
			Before administration	Start date of administration Week 12	Week 13 after administration Week 52
Background	ID number (other than Medical Chart Number)	●			
	Gender	●			
	Age (at the time when the treatment with this product is commenced)	●			
	Inclusion criteria	●			
	Start date of administration (Western calendar)	●			
	Height/Weight		●		
	Hospitalization status (inpatient/outpatient)		●		
	Disease to be studied/duration of disease		●		
	Depression phase (initial onset/relapse)		●		
	Duration of the latest episode		●		
	Presence or absence and severity of hepatic impairment		●		
	Presence or absence and severity of renal impairment		●		
	Drinking status		●		
	Medical history (prior and present)		●		
	Presence or absence of past suicidal ideation or suicide attempt		●		
Targeted drug use record (actual dosing record)				◄——►	
Discontinuation record				●[1)]	●[1)]
Prior medications/concomitant drug therapies for depression/depressive state			◄——	——►	——►
Other concomitant drug therapies			◄——	——►	——►
Prior and concomitant non-drug therapies for depression/depressive state			◄——	——►	——►
Blood pressure/pulse rate (sitting position)			◄——	——►	——►
CYP2D6 metabolizing-enzyme expression type[2)]			◄——	——►	——►

[redacted]

Laboratory test (blood test)		◄	———	——►
Clinical assessment (HAM-D)		◄	———	——►
Clinical assessment (MADRS)		◄	———	——►
Overall severity (CGI-S)		◄	———	——►
Overall improvement (CGI-I)			◄ ———	——►
Presence or absence of pregnancy (only for women)			◄ ———	——►
Confirmation of presence or absence of safety specifications and adverse events corresponding to other safety specifications			◄ ———	——►
Adverse events (all adverse events)			◄ ———	——►

[1)] If the study was not continued until completion of the observation period of this case report form
[2)] If the investigator has obtained the information on CYP2D6 by PM/IM/EM/UM in daily medical practice

7.3.1. Patient Background

1) Input the information at the commencement of this product into the registration form
   1. ID number (other than Medical Chart Number)
   2. Gender (male/female)
   3. Age (at the time when the treatment with this product is commenced)
   4. Inclusion criteria
   5. Start date of this product (Western calendar)

2) Enter the following information at the start of treatment with this product in the case report form.
   1. Height (cm), Weight (kg)
   2. Hospitalization status (inpatient/outpatient)
   3. Disease to be studied (name of disease [diagnosis] indicated for treatment with this product) and duration of disease
   4. Depression phase (initial onset/relapse)
   5. Duration of the latest episode
   6. Presence or absence and severity of hepatic impairment: If the patient has hepatic impairment, classify the severity with reference to the following criteria.

Reference) Rough guide for determination on the severity of hepatic impairment

Severity / Test item	Mild	Moderate	Severe
Total bilirubin (mg/dL)	≥1.6 - <3.0	≥3.0 - <10	≥10
GOT, GPT (U)	≥1.25×N - <2.5×N ≥50 - <100	≥2.5×N - <12×N ≥100 - <500	≥12×N ≥500
Al-P	≥1.25×N - <2.5×N	≥2.5×N - <5×N	≥5×N
γ-GTP	≥1.5×N	—	—
LDH	≥1.5×N	—	—
PT	—	—	≤40%
Symptom, etc.	—	Jaundice Hepatomegaly Hypochondrium pain right Hepatic steatosis	Bleeding tendency, symptoms of hepatic failure such as consciousness disturbed (fulminant hepatitis), cirrhosis, liver tumor, jaundice that persists for more than 6 months

N: Upper limits of normal (ULN) for each site
(Source: Classification Criteria for Severity of Adverse Reactions, Notification No. 80 of the PAB/Safety Division dated June 29, 1992)

7. Presence or absence and severity of renal impairment: If the patient has renal impairment, classify the severity with reference to the following criteria.

Reference) Rough guide for determination on the severity of renal impairment

Severity / Test item	Mild	Moderate	Severe
BUN (mg/dl)	>1×N - <25	≥25 - <40	≥40
Creatinine (mg/dL)	>1×N - <2	≥2 - <4	≥4
Urine protein	1+	2+ - 3+	>3+
Hematuria	Microscopic	Gross	Gross, clot
Urine output	—	≤500 mL/24 hr or oliguria/polyuria*	≤100 mL/24 hr or anuria
Serum potassium	—	≥5.0 - <5.5	≥5.5

[redacted]

(mEq /l)			
Other symptom, etc.	—	—	Nephrotic syndrome Acute renal failure (interstitial nephritis, tubular necrosis, renal necrosis, renal papillary necrosis, renal cortical necrosis) Chronic renal failure (interstitial nephritis, tubular necrosis, renal necrosis, renal papillary necrosis, renal cortical necrosis) Uremia Hydronephrosis

N: Upper limits of normal (ULN) for each site
Note) *Polyuria: Refer to the case of nephrogenic diabetes insipidus
(Source: Classification Criteria for Severity of Adverse Reactions, Notification No. 80 of the PAB/Safety Division dated June 29, 1992)

Important supplementary information: Hepatic impairment/renal impairment refer to an event that requires clinical attention and follow-up rather than a transient laboratory test abnormality.

8. Drinking status (frequency of drinking, amount of drinking per day)
9. Medical history (information on diseases other than those to be studied): Enter chronic diseases (including allergy), diseases that require treatment, diseases or disorders accompanied by surgery, hospitalization and/or sequela, and other potentially significant diseases or syndromes. Enter "prior" if the disease had been cured prior to the start of treatment with this product and "present" if the patient is being affected at the start of treatment with this product. However, enter the details in the adverse event section if the patient was affected with or developed the disease after the start date of treatment with this product.
10. Presence or absence of past suicidal ideation or suicide attempt

7.3.2. Administration record of targeted drug (actual dosing record)

Enter the dose, frequency of daily dosing, and treatment period of this product from the start date of treatment until the end date of observation period in this case report form (Week 12 and Week 52, or last date of treatment with this product if the treatment is discontinued). If there is any change in the dose and frequency of daily dosing, or if the treatment with this product is temporarily interrupted (washout), enter the "reason for change/washout" together.

1. Reason for change/cessation of this drug
2. Daily dose
3. Number of doses per day
4. Treatment period

7.3.3. Discontinuation record

If the study was not continued until the completion of observation period in this case report form, select the reason from the following choices and enter it as the record of study discontinuation. If "Adverse event" is chosen as the reason, enter the details in the adverse event section. If "Other" is selected, enter the reason as well.

1. Insufficient clinical effectiveness
2. Adverse event
3. No re-visit
4. Other

(Enter the reason for "Other"; for example, patient's will not related to adverse event, etc.)

[redacted]

7.3.4. Previous treatments and concomitant drug therapies for depression/depressive state

Enter the medications other than this product used for the treatment of depression/depressive state from 4 weeks prior to the start date of treatment with this product until the last date of observation period in this case report form (Week 12 and Week 52, or 28 days after the last date of treatment with this product if the treatment is discontinued).

1. Drug name (product name)
2. Route of administration
3. Daily dose
4. Treatment period

7.3.5. Other concomitant drug therapies

Enter other medications (medications other than those used for the treatment of depression/depressive state) used from the start date of treatment with this product until the last date of observation period in this case report form (Week 12 and Week 52, or 28 days after the last date of treatment with this product if the treatment is discontinued).

1. Drug name (product name)
2. Route of administration
3. Treatment period

7.3.6. Previous and concomitant non-drug therapies for depression/depressive state

Enter the non-drug therapies given from 4 weeks prior to the start date of treatment with this product until the last date of observation period in this case report form (Week 12 and Week 52, or 28 days after the last date of treatment with this product if the treatment is discontinued).

1. Name of non-drug therapy
2. Duration of non-drug therapy

7.3.7. Tests

Enter the test results for clinical course from baseline (before the start of treatment with this product) until the last date of observation period in this case report form (Week 12 and Week 52, or 28 days after the last date of treatment with this product if the treatment is discontinued). For the entry of test results before the start of treatment with this product, enter the results of the tests conducted immediately prior to the start of treatment (including the start date of treatment). For the entry of test results during the follow-up period, enter the test dates and items tested. For clinically significant abnormal fluctuations of test values compared with baseline, enter the details in the adverse event section.

7.3.7.1. Blood pressure/pulse rate (sitting position)

1. Blood pressure (systolic and diastolic blood pressure)
2. Pulse rate

7.3.7.2. CYP2D6 metabolizing-enzyme expression type

If the investigator has obtained the information on CYP2D6 by PM/IM/EM/UM in daily medical practice, enter the results.

7.3.7.3. Laboratory test (blood test)

Items to be entered: WBC count, platelet count, hemoglobin, AST (GOT), ALT (GPT), LDH, GGT (γ-GTP), Al-P, CK (CPK), total bilirubin, BUN, serum creatinine, sodium, triglycerides (TG), total cholesterol, HDL cholesterol, LDL cholesterol, fasting blood glucose, HbA1c

7.3.8. Clinical assessments

Enter the results of clinical assessment obtained from the following rating scales.

[redacted]

7.3.8.1. HAM-D

As a clinical assessment, enter the assessment results of 17 items for the Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$). Among the assessments conducted within 4 weeks prior to the start of treatment with this product, enter the assessment results closest to the start date of treatment and results of assessments conducted until the first visit after the end date of the observation period (Week 12 and Week 52). If the treatment with this product is discontinued, enter the results of assessment conducted on the start date of tapering. However, if there are no assessments during the applicable period, enter the results of assessments close to the applicable period. Also, enter the assessment results if the subject had the follow-up visits and assessments until the last date of observation period, and if the assessments were conducted before and after each dose escalation. Assessments should be conducted approximately 4 weeks after dose escalation. However, if there are no assessments during the applicable period, enter the results of assessments after dose escalation close to the applicable period.

1. Presence or absence of HAM-D rating (if "No" is selected for the rating prior to the treatment with this product, enter the reason)
2. Rating date of HAM-D
3. Rating of each item of HAM-D

7.3.8.2. MADRS

As a clinical assessment, enter the assessment results of Montgomery - Asberg Depression Rating Scale (MADRS). Among the assessments conducted within 4 weeks prior to the start of treatment with this product, enter the assessment results closest to the start date of treatment and results of assessments conducted until the first visit after the end date of the observation period (Week 12 and Week 52). If the treatment with this product is discontinued, enter the results of assessment conducted on the start date of tapering. However, if there are no assessments during the applicable period, enter the results of assessments close to the applicable period. Also, enter the assessment results if the subject had the follow-up visits and assessments until the last date of observation period, and if the assessments were conducted before and after each dose escalation. Assessments should be conducted approximately 4 weeks after dose escalation. However, if there are no assessments during the applicable period, enter the results of assessments after dose escalation close to the applicable period.

1. Presence or absence of MADRS rating (if "No" is selected for the rating prior to the treatment with this product, enter the reason)
2. Rating date of MADRS
3. Rating of each item of MADRS

7.3.9. Clinical global impressions (CGI)

Enter the results of assessments obtained from the following rating scales for impressions by the clinician (clinical global impressions).

7.3.9.1. Overall severity (CGI-S)

The CGI-S is a 7-point rating scale that rates the overall severity of an illness. The investigator enters the assessment results before the start date of treatment with this product (within 4 weeks before the start of treatment) and results of assessments conducted until the first visit after the end date of the observation period (Week 12 and Week 52). If the treatment with this product is discontinued, enter the results of assessment conducted on the start date of tapering. However, if there are no assessments during the applicable period, enter the results of assessments close to the applicable period. Also, enter the assessment results if the subject had the follow-up visits and assessments until the last date of observation period, and if the assessments were conducted before and after each dose escalation. Assessments should be conducted approximately 4 weeks after dose escalation. However, if there are no assessments during the applicable period, enter the results of assessments after dose escalation close to the applicable period.

1. Presence or absence of CGI-S rating (if "No" is selected for the rating prior to the treatment with this product, enter the reason)
2. Rating date of CGI-S

3. Rating points of CGI-S
・1: Normal, not at all ill
・2: Borderline mentally ill
・3: Mildly ill
・4: Moderately ill
・5: Markedly ill
・6: Severely ill
・7: Among the most extremely ill patients

7.3.9.2. Overall improvement (CGI-I)

The CGI-I is a 7-point rating scale that rates the overall improvement of an illness regardless of whether or not the change is attributed to drug therapy. The investigator enters the results of assessments conducted until the first visit after the end date of the observation period (Week 12 and Week 52) on the changes compared with baseline (including the start date of treatment). If the treatment with this product is discontinued, enter the results of assessment conducted on the start date of tapering. However, if there are no assessments during the applicable period, enter the results of assessments close to the applicable period. Also, enter the assessment results if the subject had the follow-up visits and assessments until the last date of observation period, and if the assessments were conducted before and after each dose escalation. Assessments should be conducted approximately 4 weeks after dose escalation. However, if there are no assessments during the applicable period, enter the results of assessments after dose escalation close to the applicable period.

1. Rating points of CGI-I (Enter the reason for “unevaluable” if the assessment cannot be made.)
・1: Markedly improved
・2: Moderately improved
・3: Mildly improved
・4: Unchanged
・5: Slightly worsened
・6: Worsened
・7: Severely worsened

7.3.10. Pregnancy status

Enter the presence or absence of pregnancy from the start date of treatment with this product until the last date of observation period.

7.3.11. Confirmation of presence or absence of safety specifications and adverse events corresponding to other safety specifications

Confirm presence or absence of safety specifications and adverse events corresponding to other safety specifications from the start date of treatment with this product until the last date of observation period and enter the results.

7.3.12. Adverse events

Regardless of the causal relationship with this product, enter the following information on all adverse events which occurred from the start of treatment with this product until the end date of observation period in this case report form (28 days after the last date of treatment if the treatment is discontinued) in the adverse event section.
・Presence or absence of adverse event
・Adverse event term
・Onset date
・Action taken
・Seriousness
・Outcome of adverse event to date

・Causal relationship with this product

If any adverse events related to abnormal fluctuations of test values such as laboratory tests and physiological tests occurred, enter the following information in the test related to adverse event section.
・Test name
・Reference value at site
・Unit
・Date of measurement
・Test result

Note: An adverse event is any untoward medical occurrence in a patient following dose of this product (including clinically significant abnormal change in laboratory test results); the event need not necessarily to have a causal relationship with the treatment. A serious adverse event is any untoward medical occurrence that results in death, is life-threatening (immediate risk of death), requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, results in congenital anomaly/birth defect, or may result in other medically important event or disorder.

7.3.13. Major investigation items

Serotonin syndrome, Convulsion, Withdrawal syndrome, Increased blood pressure/Hypertensive crisis/Increased heart rate, QT prolongation/Torsade de Pointes (TdP), Lipid effects, Hyponatremia/Syndrome of inappropriate secretion of antidiuretic hormone (SIADH), Stevens-Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN)/Erythema multiforme, Anaphylaxis, Urinary retention, Suicidal ideation/Suicide attempt, Mania/Hypomania, Abnormal Bleeding: ecchymoses, hematomas, epistaxis, and petechiae leading to life-threatening hemorrhage, Hostility/Aggression, Ischaemic heart disease, Agranulocytosis/Aplastic anaemia/Pancytopenia/Neutrophil count decreased/Platelet count decreased, Interstitial lung disease (ILD), Noradrenaline effect potentiation by increase in dosage (Insomnia, Blood pressure increased, etc.), Safety in the patient with mild or moderate hepatic impairment, Safety in the patient with mild or moderate renal impairment.

7.4. Data sources

This study will extract information necessary for doctors based on the protocol by using the information in medical charts.

7.5. Target sample size

7.5.1. Planned sample size

900 subjects who completed the 12-week treatment with this product

7.5.2. Rationale for sample size

The drug use investigation will be conducted in the registration cases of 1,200 subjects with the target sample size of 900 subjects who complete the 12-week treatment with this product and the observation period for up to 52 weeks (1 year). The information will be collected from about 400 subjects who complete the 52-week treatment with this product. In this study, the occurrence of adverse events regardless of the treatment period will be confirmed for the first 12 weeks after the treatment with this product and the safety for up to 52 weeks will be also confirmed.

Based on the final tabulation of the drug use investigation of Jzoloft Tablets conducted by our company, it was reported that 839 subjects (27.4%) discontinued the treatment until Week 16 among the 3,064 subjects included in the safety analysis[1)]. Assuming the percentage of subjects who continue to use this product at 75% based on the discontinuation rate in the drug use investigation of Jzoloft Tablets, we estimated that about 900 subjects who continue to use this product for 12 weeks could be collected by

conducting this study for 1,200 subjects with the target sample size of 900 subjects who complete the 12-week treatment.

Based on the final tabulation of the special investigation (long-term use investigation) of Jzoloft Tablets conducted by our company, there were 369 subjects (34.5%) who continuously used this product for 52 weeks among the 1,069 subjects included in the safety analysis[2)]. Assuming the percentage of subjects who continue to use this product at 30% based on the continuation rate for 52 weeks in the special investigation of Jzoloft Tablets, it is considered that we can collect about 400 subjects who continue to use this product for 52 weeks by conducting this study for 1,200 subjects.

[1)] Including some subjects who were registered as having panic disorder.

[2)] It is a similar drug and in the special investigation (long-term use investigation) of Jzoloft Tablets conducted by our company, the contract for special investigation was concluded with some sites which conducted the drug use investigation and, among the subjects registered in the drug use investigation, all subjects who continued to receive the drug for 16 weeks or longer were registered. For this reason, the target sample size was set to be 1,069 subjects by adding the subjects who discontinued the treatment before Week 16 to those who were registered in the special investigation in order to derive the continuation rate.

7.6. Data management

7.6.1. Data collection method

In this study, the data entry in the case report forms and data confirmation will be conducted by using online electronic post-marketing data collection system (or EDC, hereinafter referred to as this system) provided by the sponsor.

7.6.2. Patient registration

The investigator enters the registration items in the patient registration screen in this system and sends them after e-signing. The case registration must be conducted within 14 days including the start date of treatment with this product.

7.6.3. Reminders concerning completion, revision, and submission of case report form

7.6.3.1. Data entry

The investigator confirms the investigation items, enters the data in this system based on the information in medical charts, and sends them after e-signing.

7.6.3.2. Data revision

If there is any inquiry about the entry from the sponsor (re-investigation), the investigator confirms the information in medical charts again, corrects and re-submits it when necessary.

7.6.3.3. Submission

The investigator should send the data promptly after the entry according to the procedures stipulated by the sponsor.

7.7. Data analysis

1) Definition of analysis set
   The subjects who are confirmed to have received treatment with this product are included in the safety analysis set. The subjects who are evaluable (those considered to have appropriate

assessments) according to the analysis plan separately stipulated are included in the efficacy analysis set.

2) Analytical method
   (1) Safety analysis
   For the safety analysis set, major analysis items include occurrence of major adverse reactions and incidence of adverse reactions (percentage of patients with adverse events for which the causal relationship with this product cannot be ruled out).
   (2) Efficacy analysis
   For the efficacy analysis set, major analysis items include those prescribed in the sections of clinical assessments and clinical global impressions (CGI).

The detailed method of statistical analysis for the data to be collected in this study will be described in the statistical analysis plan of this study and kept by Pfizer. While a plan outlined in the protocol may be changed in the statistical analysis plan, any important change in the definition or analysis of the primary endpoint must be reflected in the revision of the protocol.

7.8. Quality control

Prior to the implementation of this study, the site staff will explain the contents of the protocol, etc. to the investigator and request him/her to prepare a case report form based on the medical chart.

7.9. Limitations of the research methods

This study may have the following limitations.
1) Since no control group is set in this study, there is a limitation in judgment on whether the risk of onset of adverse events or adverse reactions increases with the drug administered.
2) Since the background information on patients cannot be adequately collected in some cases, consideration of confounding factor may be insufficient.
3) Since this is the study to collect the medical chart information, the target data may not be collected or missing.

7.10. Other aspects

N/A

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient information and consent

All the staff involved in this study must guarantee to protect the personal information of patients to be investigated and make sure that any forms, reports, publications provided by Pfizer and other documents that may be disclosed will not contain the names of patients unless otherwise required by laws. Pfizer will keep high-level confidentiality and protect the personal information when transferring the data.

In this study, the information will be collected by transcribing the medical chart information described in daily clinical practice. Since the information collected from the medical chart is anonymized and does not contain the information that can identify an individual patient, the consent form will not be used.

8.2. Patient withdrawal criteria and procedure

N/A

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

The review by Institutional Review Board (IRB)/Independent Ethics Committee (IEC) is not mandatory in this study.

8.4. Ethical conduct of the study

Since this study is conducted within the scope of the "Ministerial Ordinance on Good Post-marketing Study Practice for Drugs" (MHLW Ordinance No. 171 dated December 20, 2004), ethical conduct of the study is not applicable.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Handling of each event when the investigator becomes aware of any event related to the safety information will be stipulated below.

An event that needs to be reported to the sponsor within 24 hours should be reported using the designated AE report form (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.

If any AE is observed, the investigator must take appropriate measures, quickly inform Pfizer (hereinafter referred to as "sponsor"), and if the causal relationship with this product cannot be ruled out, follow it until the AE or its sequela resolves or becomes stable to a degree considered acceptable by the investigator and the sponsor.
Also, for patients with a serious adverse reaction or adverse reaction not described in the package insert, etc., the detailed investigation will be conducted separately if the sponsor considers it necessary.

9.1. Requirement

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 events	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 this product, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

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 AE);

- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

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

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

Abnormal test findings

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

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in dosing or discontinuation of the treatment with this product, 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 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.

[redacted]

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;
- 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 any of the 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 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 another 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/subject has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical condition (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 the study (e.g., for a test or procedure required by the study protocol)

9.4.3. Scenarios reportable to Pfizer Safety within 24 hours

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

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

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

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

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 breast feeding

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;

[redacted]

- 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 ISSUE

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 this study protocol that the investigator becomes aware of.

11. ORGANIZATIONAL SYSTEM FOR STUDY IMPLEMENTATION

It will be the same as Attachment "Organization system for post-marketing surveillance and equivalent activities." Study Manager shall be the Director of Post Marketing Study Strategy and Management.

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

Address: Shinjuku Bunka Quint Bldg., 3-22-7 Yoyogi, Shibuya-ku, Tokyo
Company name: Pfizer R&D Japan G.K.
Scope of subcontract: Operations concerning the planning of surveillance, preparation of draft plan, operation, etc. of the surveillance

Address: 2-23 Shimomiyabi-cho, Shinjuku-ku, Tokyo

[redacted]

Company name: EPS Corporation
Scope of subcontract: Among the operations for this study, those excluding the management operations for post-marketing surveillance, etc. such as registration and reception and data management

Address: 2-4-32 Aomi, Koto-ku, Tokyo
Company name: Fujitsu FIP Corporation
Scope of subcontract: Operations concerning the establishment, operation, etc. of the post-marketing surveillance data collection system

13. ADDITIONAL MEASURES WHICH MAY BE TAKEN BASED ON THE RESULTS OF INVESTIGATION AND CRITERIA FOR DETERMINATION ON 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 ASSESSMENTS OF THE IMPLEMENTATION STATUS OF THIS STUDY AND OBTAINED RESULTS OR REPORTING TO THE PMDA

Safety assessment and reporting will be made at the time of Periodic Safety Report and completion of the study.

15. OTHER ASPECTS

1) Revision of protocol

Based on new knowledge to be obtained with the progress of this study, the need to revise the protocol should be reviewed and the protocol should be revised whenever necessary. The need to revise the protocol should be reviewed and the protocol should be revised whenever necessary if the approval for partial change in the dosage and administration or indications, etc. is obtained during the reexamination period (excluding the case where the reexamination period is newly designated).

2) Measures to be taken if any problem or question is observed

Revision of the package insert and implementation of new special investigation and/or post-marketing clinical study should be considered if onset of a serious and unexpected adverse reaction is suggested, a significant increase in the incidence of adverse reactions is observed, any concern for the efficacy and safety of the drug is found compared to before the approval, and onset of a different adverse reaction is suggested, etc.

CC
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CCI	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

17. REFERENCES

N/A

18. LIST OF TABLES

19. LIST OF FIGURES

20. LIST OF STAND ALONE DOCUMENTS

N/A

21. ADDITIONAL INFORMATION

The sources of the investigation form in which the results of clinical assessment will be entered are the all item assessment forms shown below.

1) HAM-D
STAR*D Version SIGH-D (excerpted version from the Japanese version of Structured Interview Guide for Combined Rating of HAM-D and IDS-C) ver.1.1

Edited by Toshiya Inada, authored by Toshiya Inada, Koichi Sato, Nobutomo Yamamoto, Ataru Inagaki, Gohei Yagi, and Yoshibumi Nakane: Make full use of HAMD - illustration and usage guide for Hamilton Rating Scale for Depression (HAMD). Seiwa Shoten, first printing of first edition issued on April 20, 2014, included

2) MADRS
MADRS Rating Training Sheet by SIGMA ver.1.2
Second printing of revised version (ver.1.2) (bundle version) issued on January 15, 2009, illustrated by Toshiya Inada, Nagahide Takahashi, issued by The Japanese Society of Psychiatric Rating Scales

DVD editorial supervisor and author Toshiya Inada, academic instruction by Norio Ozaki and Teruhiko Higuchi, DVD preparation discussion members Nagahide Takahashi and Toshiya Inada: Clinical assessment of depression with the Japanese version of MADRS using SIGMA -Japanese version of Montgomery-Åsberg Depression Rating Scale (MADRS) training DVD. The Japanese Society of Psychiatric Rating Scales, issued on June 30, 2006, included