Lyrica® Capsule

Special Investigation

- Investigation on the Use in Patients with Fibromyalgia -

Protocol

Pfizer Japan Inc.

[redacted]

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[redacted]

Introduction

Pregabalin, an active ingredient of Lyrica Capsule (hereinafter called “the product”) is one of the derivatives of γ-aminobutyric acid (GABA) developed at Northwestern University, USA.

In the excessively stimulated excitable nervous system, pregabalin binds with high affinity to α2δ protein (an auxiliary subunit of voltage-gated calcium channels), which supposedly reduces calcium inflow into presynaptic nerve terminals and suppresses the synaptic release of excitatory neurotransmitters, consequently leading to manifestation of analgesic activity.

As of February 2012, the product has been approved for indications of neuropathic pain (peripheral neuropathic pain and central neuropathic pain) and the like in 120 countries of the world, including the US, European Union countries, Australia and Canada. In Japan, the product has been approved for indications of peripheral neuropathic pain in October 2010, and pain associated with fibromyalgia in June 2012.

The special investigation on Lyrica Capsule (hereinafter called “the survey”) will be undertaken to collect or check information about the incidence of each type of disorder arising from adverse reactions to the product and the information on quality, efficacy and safety of the product in routine clinical use. The information collected through the survey will be supplied as the information on proper use of the product to medical facilities and used to prepare the application materials for reexamination of the product. To this end, the survey needs to be carried out in compliance with the Good Post-marketing Surveillance Practice (Ministry of Health, Labour and Welfare [MHLW] Ordinance No. 171, dated December 20, 2004). The case data collected through this survey will be reported to the MHLW pursuant to the Pharmaceutical and Medical Device Act. If applicable, the data including names of drugs, adverse reactions, gender and age by decade may be disclosed as a listing of patients in the “Pharmaceuticals and Medical Devices Safety Information” and “Pharmaceuticals and Medical Devices Information Website (http://www.info.pmda.go.jp)” which are issued and managed, respectively, by the MHLW. The collected case data may be also disclosed if the MHLW is requested to disclose them pursuant to the “Act on Access to Information Held by Administrative Organs” (Act No. 42, dated May 14, 1999). In any of the above cases, the report does not cover the name of the physicians, facilities or the like involved, and these pieces of information will never be published or disclosed.

1 Objectives

The objectives of this survey are to obtain information about (1) the incidence of adverse reactions to the product under actual use conditions, and (2) the factors which may affect the safety and efficacy of the product in routine clinical practice for patients with fibromyalgia.

The following events will be evaluated as major investigation items;

- Peripheral edema and edema-related events*
- Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury
- Vision-related events

*: Adverse events of the cardiovascular and respiratory systems will be also checked.

2 Study population

Patients with a diagnosis of fibromyalgia. The patients should not have used the product before the survey.

The standards used for the diagnosis of fibromyalgia will be also checked.
(International diagnostic criteria: (i) Classification Criteria for Fibromyalgia of American College of Rheumatology [ACR] 1990, (ii) Preliminary Diagnostic Criteria for Fibromyalgia of ACR 2010(*), (iii) Fibromyalgia Activity Scale [FAS-31], (iv) others [e.g., revision of (*)])

The indications, dosage and administration of the product for fibromyalgia are specified below:

Indication: Pain associated with fibromyalgia	
Dosage and Administration:	The usual starting dose in adults is 150 mg/day of pregabalin orally administered in 2 divided doses, which may be gradually increased to 300 mg/day over one week or longer. Subsequently, the dose is maintained at 300 to 450 mg/day. The dose may be adjusted depending on age and symptoms as appropriate, provided the daily dose may not exceed 450 mg and the product should be orally administered in 2 divided doses regardless of the daily dose. The latest version of the package insert should be referred to when the product is prescribed.

3 Target sample size

The target sample size is 500 patients. At least 50 male patients with fibromyalgia will be included in the survey.

[Rationale]
The adverse reactions included in the major investigation items for the product and the incidence in 250 patients with fibromyalgia treated with pregabalin in the phase 3 study conducted in Japan (Study No. A0081208, 16 weeks) were as follows: peripheral edema (17 patients, 6.8%), edema (3 patients, 1.2%), dizziness (72 patients, 28.8%), somnolence (113

patients, 45.2%), loss of consciousness (1 patient, 0.4%), syncope (0 patient, 0%), and vision-related events (23 patients, 9.2%). These results suggested that there are no significant difference in anticipated risks between the population with peripheral neuropathic pain and the population with fibromyalgia. Thus, the safety profile of the product in patients with fibromyalgia will be investigated by comparing the results of the present survey with the adverse reaction profiles in the currently ongoing drug use investigation in 3000 patients with peripheral neuropathic pain. The target sample size of 500 patients is expected to have a 95% or higher probability to detect adverse reactions occurring at the incidence of 1% or higher, which include peripheral edema, edema, dizziness, somnolence, and vision-related events.

4 Planned survey period

The survey period and the period for registration into the survey are specified below:
Survey period: December 2012 to September 2016
Registration period*: December 2012 to September 2015

*: Patient registration will be continued until the number of registered patients reaches the target sample size.

5 Survey procedures

5.1 Survey method

The survey will be conducted with the central registration system.

5.2 Data collection method

In this survey, data will be collected using the survey form provided by Pfizer Japan Inc. (hereinafter called “the sponsor”). The investigator will complete the survey forms and submit them to the sponsor during the survey.

5.3 Patient registration

(1) Registration

When the product is administered to the patients satisfying the eligibility criteria shown below, the investigator will fill in the following items for registration in the registration forms and fax them to the Registration Center to register patients until the targeted number of patients is reached. Considering that the incidence of adverse events included in the major investigation items (peripheral edema, dizziness, etc.) was highest during the early stage of treatment with the product, registration of patients should be done within 7 days as a rule (within 14 days at latest), counting the day of the start of treatment with the product as Day 1, with the aim of enabling appropriate collection of information on these adverse events.

1) Eligibility criteria

・Patients with a diagnosis of fibromyalgia.
・Patients having never used the product before the survey

2) Registration items

Basic information including name initials of the patient (as needed), ID code, gender, birth date (or age), starting date for treatment with the product and eligibility to the survey.

(2) Exclusion from registration

Patients who are found to be ineligible for registration after reception of the patient registration forms by the Registration Center will be excluded from registration.

[Registration Center]

ACRONET Co., Ltd
FAX number: +81-120-770-190 (toll-free)

5.4 Observation period

The observation period will start on the first day of treatment with the product (Day 1) and last until Week 52 (Day 364).

For patients who are continuing treatment as of Week 52, safety will be evaluated on the day of the first visit after the end of the observation period (including the last day of the observation period), and safety information will be collected.

In cases where treatment has been completed or discontinued before Week 52, safety will be evaluated until the day of the first visit following 7-day period after the completion (discontinuation) of treatment, and safety information will be collected for this period.

Completion of treatment means cases where further treatment with the product is judged unnecessary because of achievement of the purpose of treatment set at the start of treatment (e.g., cure of target diseases).

5.5 Precautions in completion of survey form, correction and confirmation

(1) Completion of survey form

The investigator should check each survey item and write down data using an inerasable pen or ballpoint pen, on the basis of the records of healthcare (medical records, test reports, etc.). Data entry sample etc. should be referred to for detailed procedure.

(2) Data correction

The investigator should correct entries by drawing double strikethrough (=) on the mistake and affix a seal on the strikethrough while keeping the original entries legible. If the sponsor places inquiry about the entered information, the investigator should check the above-mentioned healthcare records again and, as needed, correct the information on the survey form and submit the form again. When any information related to evaluation of efficacy and safety is corrected, the reason for correction and the date of correction should also be entered in principle.

(3) Data confirmation

Upon completion of entry and correction of all survey data, the investigator should check the information on the completed survey form and the re-inspection form again. The investigator should print his/her name and affix a seal, or instead put his/her signature, on the checked form.

6 Items and time of survey

The investigator will conduct the survey in accordance with the observation schedule given below. After conclusion of the contract on the survey, the investigator will register eligible patients. Then, the investigator will check the data on each registered patient (including the data on background variables at the start of treatment) and fill in the survey form for each patient.

[Observation schedule]

		Registration form	Survey form				
Survey items \ Time point of observation		At registration[1)]	Observation period: Start of treatment	Week 4	Week 13	Week 26	Week 52 (or completion/ discontinuation)
Identifiable patient information	ID code	●	○				
	Name initials (not indispensable)	●	○				
	Gender	●	○				
	Birth date (age)	●	○				
	First day of treatment with the product	●					
	Eligibility	●					
Background variables	Height/body weight[2)]		●				
	Hospitalization status (inpatient/outpatient)		●				
	Target disease, severity, duration		●				
	Tender points based on “ACR 1990 Criteria for Classification of Fibromyalgia”		●				
	Widespread pain index (WPI) and symptom severity (SS) scores based on “Fibromyalgia Activity Scale (FAS-31)”[3)]		●				
	Presence/absence of hepatic/renal dysfunction and severity		●				
	Creatinine clearance[4)]		●				
	Presence/absence of hemodialysis		●				
	Presence/absence of ocular disease history/complications[5)]		●				
	Disease history (information other than the target disease)		●				
	History of previous treatment drugs for the target disease[6)]		●				
	Pregnancy status and date of delivery/planned date of delivery (females only)		●	←	—	—	→
	Number of days of absence from work (including housework and school) because of fibromyalgia in past four weeks		●				●
Records of treatment with the product			←	—	—	—	→
Information regarding hemodialysis (if observed)			←	—	—	—	→
Concomitant therapy (concomitant drug therapy/concomitant non-drug therapy)			←	—	—	—	→
Test	Body weight, creatinine clearance		●	●	●	●	●

	Presence/absence of withdrawal symptom/rebound phenomenon as of 7 days after completion/discontinuation[7)]						●
	Presence/absence of hyperalgesia		●				●
	Laboratory test		←	—	—	—	→
Clinical evaluation	Pain score		●	●	●	●	●
	Quality of sleep score		●	●	●	●	●
	Questionnaire about mind and body (PHQ-9)		●	●	●	●	●
	Questionnaire about health status (EQ-5D)		●	●	●	●	●
	Fibromyalgia Activity Scale (FAS-31)		●	●	●	●	●
	Japanese version of the Revised Fibromyalgia Impact Questionnaire (JFIQR)		●	●	●	●	●
	Patient's impression (PGIC)						●
	Physician's impression (CGIC)						●
Patient summary							●
Adverse events			←	—	—	—	→

● Data to be entered; ○ Printed on survey form

1): Entry at the time of patient registration. These pieces of information related to patient registration will be registered within 7 days after the start of treatment, as a rule, and within 14 days at the latest.
2): Body weight at the start of treatment will be entered in the field of "Body weight" of Tests.
3): To be entered in Clinical Evaluation [FAS-31].
4): Creatinine clearance at the start of treatment will be entered in the field of "Creatinine clearance" of Tests.
5): To be entered in Background variables (disease history).
6): The drugs previously used for the treatment of target disease in the period from 14 days to 1 day before the start of treatment with the product will be entered.
7): For patients who have completed (discontinued) administration of the product, withdrawal symptom/rebound phenomena observed in the period from the day of completion (discontinuation) of treatment to 7 days later will be entered.

6.1 Information necessary for identifying patients

The following data will be entered at the time of patient registration.

[1] Identification code*
[2] Name initials (as needed)*

*: Data to be collected on the registration form (to be printed on the survey form).

6.2 Background variables

(1) The following information will be entered as of the day of start of administration of the product.

[1] Gender*
[2] Birth date (age)*
[3] First day of treatment with the product
[4] Height
[5] Body weight
[6] Hospitalization status (inpatient/outpatient)
[7] Target disease, severity, duration
[8] Tender points based on "American College of Rheumatology (ACR) 1990 Criteria for Classification of Fibromyalgia"
[9] Widespread pain index (WPI) and symptom severity (SS) scores based on "Fibromyalgia Activity Scale (FAS-31)" (reference values)
[10] Presence/absence of hepatic/renal dysfunction and severity

[11] Creatinine clearance
[12] Whether the patient is on hemodialysis or not
[13] Presence/absence of ocular disease history/complications (This item will be entered in the field of disease history.)
[14] Disease history (information other than the target disease)

- Name of disease or syndrome
- Whether the disease is a past one or is present now.

The name of chronic disease (including allergy), disease requiring treatment, disease or disorder requiring or causing surgery, hospitalization or sequelae, and other possibly problematic disease or syndrome will be recorded. The disease or syndrome which has healed before the start of treatment with the product is counted as “past disease” and the disease or syndrome present at the start of treatment is counted as “present disease.”

[15] History of previous treatment drugs for the target disease (name, dosage form category, daily dose, administration period, and reason for discontinuation of the drugs used during the period from 14 days to 1 day before the start of treatment with the product)

*: Data to be collected on the registration form (to be printed on the survey form).

(2) The following status from the day of start of treatment with the product through the day of safety evaluation will be entered.
[1] Pregnancy status and date of delivery/planned date of delivery (females only)

(3) The following items of evaluation will be checked and record the results before the start of treatment with the product and at Week 52. In cases where treatment has been completed or discontinued before Week 52, the data at the time of completion (discontinuation) of treatment will be entered.
[1] Number of days of absence from work (including housework and school) because of fibromyalgia in past four weeks

6.3 Records of treatment with the product

The following information about the product administration until the day of safety evaluation will be entered:

[1] Daily dose
[2] Number of doses per day
[3] Timing of administration
[4] Dosing period
[5] Reason for change of dose levels

In cases receiving hemodialysis, the following information will be also entered:

[6] Frequency of dialysis
[7] Duration of each session of dialysis
[8] Supplemental dose after dialysis

6.4 Concomitant therapy

(1) Concomitant drug therapy

The following information will be entered about all drugs used by the day of safety evaluation.

Medications administered for treatment of adverse events should be also entered.

[1] Name of drug (brand name)
[2] Dosage form category
[3] Daily dose
[4] Number of doses per day
[5] Dosing period
[6] Reasons for the use of drugs

(2) Concomitant non-drug therapy

The following information will be entered about the non-drug therapies administered by the day of safety evaluation.

Non-drug therapy administered for treatment of adverse events should be also entered.

[1] Name of therapy
[2] Period of use
[3] Reason for use

6.5 Test

(1) Body weight, creatinine clearance

The following information will be entered. The body weight will be measured before the start of treatment with the product, at Week 4, Week 13, Week 26 and Week 52 and by the day of safety evaluation. If the investigator considers that the change in any of these values from the pre-treatment level is abnormal, it will be reported as an adverse event.

[1] Date of evaluation
[2] Results

(2) Presence/absence of withdrawal symptom/rebound phenomenon

For patients who have completed (discontinued) administration of the product, withdrawal symptom/rebound phenomena observed in the period from the day of completion (discontinuation) of treatment to 7 days later will be entered.

[1] Results

(3) Presence/absence of hyperalgesia

Information will be entered about the presence/absence of hyperalgesia before the start of treatment and at Week 52 or at the time point of last observation. In cases where treatment has been completed or discontinued before Week 52, the data at the time of completion (discontinuation) of treatment will be entered. If the investigator considers that the change in the condition of hyperalgesia from the pre-treatment status, it will be reported as an adverse event.

[1] Results

(4) Laboratory test

The results of the following tests conducted before the start of treatment with the product through the day of safety evaluation will be entered. The latest results of the tests conducted before the start of treatment will be entered in the field of the tests before the start of treatment with the product.

[Test items]

Serum creatinine
Serum amylase
Free thyroxine (Free T4) or serum total thyroxine (T4)
Thyroid-stimulating hormone (TSH)
Blood sugar (fasting)
Hemoglobin A1c (HbA1c)
Creatine kinase (CPK)
Triglyceride
LDL -cholesterol (LDL-Cho)
Prolactin

[Matters to be entered]

[1] Date of measurement
[2] Results

6.6 Clinical evaluation

The product is evaluated with the following items of evaluation before the start of treatment with the product and at Week 4, Week 13, Week 26, and Week 52 or at the time point of last observation, and the date and results of evaluation will be entered. In cases where treatment has been completed or discontinued before Week 52, the data at the time of completion (discontinuation) of treatment will be entered.

1) Pain score: The pain from fibromyalgia experienced during the past 24 hours will be rated at the time of getting up in the morning on a 11-grade scale, ranging from 0 (no pain) to 10 (the most severe pain possible).

2) Quality of sleep score: The quality of sleep experienced during the past 24 hours will be rated at the time of getting up in the morning on a 11-grade scale, ranging from 0 [the best sleep possible] to 10 [the worst sleep possible].)

3) Questionnaire about mind and body (Patient Health Questionnaire [PHQ-9]): Symptoms related to depression will be evaluated based on the following 9 questions: 1 (little interest or pleasure in doing things), 2 (feeling down, depressed, or hopeless), 3 (trouble falling or staying asleep, or sleeping too much), 4 (feeling tired or having little energy), 5 (poor appetite or overeating), 6 (feeling bad about yourself – or that you are a failure or have let yourself or your family down), 7 (trouble concentrating on things, such as reading the newspaper or watching

television), 8 (moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual), 9 (thoughts that you would be better off dead, or of hurting yourself).

4) Questionnaire about health status (EuroQol-5 Dimension [EQ-5D]): Health status will be evaluated based on the following 5 questions: mobility, self-care, usual activity (e.g., work, study, housework, family or leisure activities), pain/discomfort, and anxiety/depression.

5) Fibromyalgia Activity Evaluation List (FAS-31)
Widespread pain index (WPI): Applicable symptoms will be evaluated;
(Jaw [left/right], shoulder [left/right], upper arm [left/right], forearm [left/right], chest, abdomen, thigh [left/right], lower leg [left/right], neck, back [upper/lower], buttocks [left/right]).
Symptom severity (SS) Symptoms: Applicable symptoms will be evaluated;
(Having difficulty in getting over from fatigue, 0 [no problem], 1 [mild], 2 [moderate], 3 [severe]; feeling discomfort or feeling that something is wrong when getting up, 0 [no problem], 1 [mild], 2 [moderate], 3 [severe]; easily forgetting time and place, 0 [no problem], 1 [mild], 2 [moderate], 3 [severe]).
Symptom severity (SS) General physical symptoms: Applicable symptoms will be evaluated;
(Muscle pain, feeling that the abdomen is swollen/sense of distension, getting tired easily, decreased thinking ability, decreased muscle strength, headache, twitching in the upper part of the abdomen, numbness, dizziness, difficulty in falling asleep/sleep disorder, feeling melancholic, constipation, pain in the upper part of the abdomen, feeling nauseous, nervous, pain in the chest, visual impairment, pyrexia, diarrhea, dry mouth/decreased salivary secretion, itchiness, wheezing like asthma, coldness in fingers and toes, urticaria, tinnitus, vomiting, feeling sick at stomach/heartburn, stomatitis, feeling taste different than usual when eating or drinking, spasm, dry eye/decreased tear secretion, breath shortness, decreased appetite, rash, sensitive to light, having difficulty in hearing/deafness, becoming bruised easily, hair loss, going to bathroom frequently/pollakiuria, feeling pain on urination, pain in the lower part of the abdomen).

6) Japanese version of the Revised Fibromyalgia Impact Questionnaire (JFIQR)
Duration (years) after the onset of the symptoms of fibromyalgia
Duration (years) after the first diagnosis of fibromyalgia
The following activities will be evaluated: (brushing or combing hair), (walking continuously for 20 minutes), (preparing a homemade meal), (vacuuming, wiping or sweeping floor), (lifting and carrying shopping bags and other slightly heavy materials), (climbing one flight of stairs), (changing bed sheet), (sitting on a chair for 45 minutes), and (going shopping for groceries).
To what extent the following situations are true of each patient will be evaluated;

(Failing to carry out works and daily activities because of fibromyalgia), and (mentally exhausted because of fibromyalgia] will be evaluated).
Evaluation will be made concerning the following questions; How much pain did you have? How much vitality did you have? How stiff was your body? How was the quality of your sleep (how did you feel when you woke up in the morning)? How depressed did you feel? How easily did you forget? How much anxiety did you feel? How much pain did you feel when your body was pressed or touched? How much dizziness did you feel or how easily did you fall? How sensitive were you to loud sound, strong light, smell, or coldness?

The patient's and physician's impressions about the patient's condition will be evaluated at Week 52 or at the time point of last observation as compared with the impressions before the start of treatment with the product in order to evaluate the efficacy of this drug, and the date and results of evaluation will be entered. In cases where treatment has been completed or discontinued before Week 52, the data at the time of completion (discontinuation) of treatment will be entered.

7) Patient's impression (Patient Global Impression of Change [PGIC])
   1. Markedly improved
   2. Improved
   3. Slightly improved
   4. Unchanged
   5. Slightly worsened
   6. Worsened
   7. Markedly worsened

8) Physician's impression (Clinical Global Impression of Change [CGIC])
   1. Markedly improved
   2. Improved
   3. Slightly improved
   4. Unchanged
   5. Slightly worsened
   6. Worsened
   7. Markedly worsened

6.7 Patient summary

The appropriateness of continuation of treatment with the product will be checked on the day of safety evaluation. In cases where continuation of treatment with the product is not possible, one major reason should be selected from the alternatives given below. If adverse events, abnormalities in laboratory parameters or the death of patient is selected as a major reason, the information should be entered in the "adverse event" field.
In cases where treatment has been completed or discontinued before Week 52, the status at the time of completion (discontinuation) of treatment will be checked and the

data will be entered.

[1] Insufficient clinical efficacy
[2] Recovery (effective)
[3] Adverse events
[4] Abnormalities in laboratory parameters
[5] Death of patient
[6] Lost to follow-up
[7] Others

In cases where no revisit has been made after the start of treatment, it should be entered in the “Confirmation of re-visit after the start of treatment” field.

6.8 Adverse events

For evaluation of safety, the incidence of adverse events following the start of treatment with the product through the date of safety evaluation will be checked, and the following information will be entered. If any adverse event occurs, the investigator should take appropriate measures, immediately report it to the sponsor and, as a rule, observe the course and outcome of the event until disappearance of the symptom(s).
A detailed investigation will be separately carried out if patients develop serious adverse reactions or adverse reactions included in the major investigation items and the sponsor deems it necessary.
Presence/absence of adverse events related to the major investigation items, potential risks of the product (suicidal ideation [including suicide attempt and suicide after start of treatment]), and other risks (pathologic changes in appetite and activity) is checked.

[1] Day of safety evaluation
[2] Presence/absence of adverse events
[3] Name of adverse event
[4] Date of onset
[5] Measures taken
[6] Seriousness
[7] Outcome
[8] Causal relationship to the product

[The following information should be entered if the adverse event is associated with abnormal changes in test data such as laboratory tests.]

[9] Name of test
[10] Reference value at the facility
[11] Unit
[12] Date of measurement
[13] Results

Supplementary note: Adverse events mean all events unfavorable for the patient, arising after treatment with the product, regardless of presence/absence

	of causal relationship to the product (including clinically significant abnormal changes in laboratory parameters). Serious adverse events mean death, life-threatening events, and events possibly causing hospitalization, extension of hospital stay period, permanent or marked disorders/disabilities, congenital anomalies/defects or other medically significant events/disorders.

6.9 Major investigation items

The following events should be evaluated as major investigation items in this survey.

[1] Peripheral edema and edema-related events

Information will be collected about the presence/absence of events related to peripheral edema and the course of patients before and after the onset of events. The situations on development of these events will be analyzed by means of factor analysis, including analysis of the site affected, dose of the product, concomitant therapy, background variables, etc. The package insert gives precautions on congestive heart failure in patients presenting symptoms related to edema. In 30 overseas placebo-controlled studies, the incidence of hypertension and dyspnea was higher in the patients developing peripheral edema than in patients free of peripheral edema, although the incidence of the other events did not differ markedly between these two groups. In view of these facts, information on cardiac function and the incidence of adverse events of the respiratory system will be also collected.

[2] Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury

Information will be collected about the presence/absence of events related to dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury and the course of patient's condition before and after the onset of the events. The situations on development of these events will be analyzed by factor analysis, including analysis of the dose of the product, concomitant therapy, background variables and so on.

[3] Vision-related events

Information will be collected about the presence/absence of events related to the eyes and the course of patient's condition before and after the onset of the events. The situations on development of the events will be analyzed by factor analysis, including analysis of the dose of the product, concomitant therapy, background variables and so on.

Patients developing adverse events included in the major investigation items will be separately investigated in detail if the sponsor deems it necessary.

7 Items to be analyzed and analysis methods

7.1 Analysis set

Safety analysis set will include patients who satisfy the eligibility criteria and have been confirmed to have taken the product at least once. Efficacy analysis set will include patients who are evaluable for efficacy in accordance with the separately set analysis

plan (i.e., patients in whom efficacy was considered to be appropriately evaluated).

7.2 Methods of analysis

(1) Analysis for safety evaluation

In the safety analysis set, the status of onset of primary adverse reactions and incidence of adverse reactions (percentage of patients developing adverse events for which the causal relationship with the product cannot be ruled out) will be set as primary analysis items. The incidence of adverse reactions will be summarized for each factor of background variables, including gender, age, body weight, history of previous treatment drugs, and renal dysfunction, and the factors affecting the incidence of adverse reactions will be investigated. At the same time, the relationship of the incidence of adverse reactions with the timing of food intake, dose modification and reasons for dose modification will be also examined. Furthermore, changes in body weight and laboratory test values before and after administration will be examined.

(2) Analysis for efficacy evaluation

The changes in the pain score and the sleep score will be calculated. The percentages of patients showing efficacy in each of the efficacy measures (i.e., PGIC, CGIC, PHQ-9, EQ-5D, FAS-31 and JFIQR) in the efficacy-evaluable patients will be calculated. Explorative analysis will be also carried out to examine the factors of background variables affecting efficacy, such as gender, age, body weight, history of previous treatment drugs, and renal dysfunction. Another exploratory analysis will be carried out to investigate the relationship of the efficacy with the timing of food intake, dose modification and reasons for dose modification.

The detailed analysis plan is presented in the statistical analysis plan prepared separately.

8 Publication of the results

Pfizer Japan Inc. will publish the results of survey at academic society meetings, in journals and so on for the purpose of supplying information for proper use of the product.

9 Contact information

PPD

Name	PPD
Address	PPD
Fax	PPD
E-mail	PPD

10 References

Attachment 1: Adverse event report