Non-Interventional Study Protocol
A0081282

Lyrica® Capsule Special Investigation
-Investigation on Fibromyalgia-

Statistical Analysis Plan

Version: 8.0

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1. Amendments from the previous version

Version/ Date/ Author(s)	Summary of Changes/Comments
1.0/ January 31, 2014/ PPD	First version
2.0/ February 20, 2015/ PPD	**Status of survey: Ongoing** **2.1. Study Design Planned survey period** Modification associated with a change in the survey plan **5.4. Subgroup** Categories of dosage were modified to be consistent with dosage and administration. **6.1. Safety endpoints** Suicide-related events were added. **7. Handling of missing data** LOCF (Week 13 [LOCF]) assessment was added for pain score and sleep quality score. **8.2.2. Patient demographics and treatment history Information on administration of Lyrica** Categories of dosage were modified to be consistent with dosage and administration. **8.2.4. Efficacy analysis PHQ-9, EQ-5D, FAS-31, and JFIQR** Rationale for evaluation based on change was additionally specified. **8.2.3.1. Adverse reactions** Tabulation of suicide-related events was added. **A1.1 Data to be used for tabulation and analysis** The scope of data to be used was specified. **A1.2 Definition of visit schedule** Addition of the definition of Visit 1 and modification associated with the addition Definition of Week 13 (LOCF) was additionally specified. Handling of multiple observation data collected within the same visit window was additionally specified. Conditions for use in tabulation and analysis were additionally specified for efficacy evaluation. **A.2.1 Subgroup analysis** Reference population for calculation of risk ratio and risk difference as subgroup analyses of safety and efficacy was additionally specified. **Others** Description adjustment

Version/ Date/ Author(s)	Summary of Changes/Comments
3.0/ February 17, 2016 PPD	**Status of survey: Ongoing** **5. Analysis sets** Handling of patients unable to be resurveyed was changed. **6.1. Safety endpoints** Definitions of major investigation items were additionally specified. **Others** Description adjustment
4.0/ February 17, 2017/ PPD	**Status of survey: Ongoing** **6.1. Safety endpoints** Euphoric mood-related events were added as other safety endpoints. Evaluation of adverse events was added for suicide-related events. **8.2.3.1. Adverse reactions** Tabulation of major investigation item of peripheral edema and edema-related events was added. Tabulation of the relationship between dosage and administration and development of adverse reaction and the relationship between prior medications and development of adverse reactions was added. **8.2.3.3. Other endpoints** Body weight: Tabulation of adverse reactions by presence or absence of weight gain was added. **A1.1 Data to be used for tabulation and analysis** Handling of efficacy-related data was additionally specified. **Others** Description adjustment

Version/ Date/ Author(s)	Summary of Changes/Comments
5.0/ July 28, 2017 PPD	**Status of survey: Ongoing** **5.4. Subgroup** Inpatient/outpatient status at the initial prescription, past medical history and complications were added for subgroup analysis of efficacy. Definition of subgroups based on initial dose was added. **6.1. Safety endpoints** Handling of serious adverse reactions or adverse events was specified. Pancreas-related events, thyroidal function-related events, change in appetite and activity-related events, and withdrawal symptom and rebound phenomenon-related events were added as other safety endpoints. **8.1.1. Analysis of continuous data** Analysis for comparison between subgroups was changed from t-test to analysis of covariance, and the analysis method was added. **8.2.2. Patient demographics and treatment history** Tabulation of pain score (continuous data) was added as patient demographics. Tabulation of patient demographic to be performed in subgroups based on initial dose was added. Tabulation of daily dose (continuous data) and final daily dose was added as the information on administration of Lyrica. **8.2.3.1. Adverse reactions** Tabulation categories were added in the tabulation of major investigation item of dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury. Tabulation of pancreas-related events, thyroidal function-related events, change in appetite and activity-related events, and withdrawal symptom and rebound phenomenon-related events was added. Tabulation of patients with special background was added. **8.2.3.5. Exploratory analysis (safety)** Tabulation to be performed in subgroups based on initial dose was added. **8.2.4.1. Pain score** Tabulation of responders was added. **8.2.4.9. Subgroup analysis (efficacy)** Analyses for comparison between subgroups using an analysis of covariance model were additionally specified. **8.2.4.10. Exploratory analysis (efficacy)** Tabulation to be performed in subgroups based on initial dose was added. **Listings** Listings (listings of initial dose and patient demographics, etc.) were added. **Others** Description adjustment

Version/ Date/ Author(s)	Summary of Changes/Comments
6.0/ December 26, 2017/ PPD	**Status of survey: Survey completed** **6.1. Safety endpoints** Skin disorder-related events were added. **8.2.1. General description of patients** Modified to conduct the safety analysis set only in the tabulation by timing in the summary of discontinuation and dropouts. **8.2.2. Patient demographics and treatment history** Modified to use information on past medical history and complications in view of consistency, etc. among surveys for clinical findings related to major investigation items at the start of treatment as patient demographics (as the tabulation of patient demographics by subgroup based on initial dose). Definition of analgesics, etc. was added as concomitant medications at the start of treatment. Details of the method of tabulation of daily dose (continuous data) were added as the information on administration of Lyrica. **8.2.3.1. Adverse reactions** Modified to review the definition of major investigation item of peripheral edema and edema-related events to be used for detailed investigation. Tabulation of skin disorder-related events was added. **8.2.3.4. Subgroup analysis (safety)** Added tabulation to be performed based on factors showing a significant difference by testing to evaluate the relationship between patient demographics, etc. and development of adverse reactions. **Listings** Listing of events of major investigation items was deleted (the European risk management plan should be referred to as necessary because events to be handled as major investigation items are defined as Safety Specification in the European risk management plan of Lyrica). **Others** Description adjustment

Version/ Date/ Author(s)	Summary of Changes/Comments
7.0/ February 13, 2018/ PPD	**Status of survey: Survey completed** **8.2.3.1. Adverse reactions** For patients with special background, pediatric patients were additionally specified and tabulation of serious adverse reactions was added. **8.2.3.4. Subgroup analysis (safety)** Added tabulation to be performed based on factors showing a significant difference by testing to evaluate the relationship between patient demographics, etc. and development of adverse reactions. **8.2.4.9. Subgroup analysis (efficacy)** Added tabulation to be performed based on factors showing a significant difference by testing to evaluate the relationship between patient demographics, etc. and efficacy. **Others** Description adjustment
8.0/ March 9, 2018 PPD	**Status of survey: Survey completed** **6.1. Safety endpoints** Accident-related events were added as other safety endpoints. **8.2.3.4. Subgroup analysis (safety)** Added tabulation to be performed based on factors showing a significant difference by testing to evaluate the relationship between patient demographics, etc. and development of adverse reactions.

2. Introduction

This statistical analysis plan describes a plan of statistical analysis to be performed in the special investigation of Lyrica® Capsule (hereinafter referred to as Lyrica). In this plan, sentences cited from the protocol are shown in *italic*.

2.1. Study design

Study population

• *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 Lyrica should be orally administered in 2 divided doses regardless of the daily dose.*

- *Study population: The survey covers the patients satisfying all of the following requirements:*
- *Patients with a diagnosis of fibromyalgia.*
- *The patients should not have used Lyrica before the survey.*

The standards used for the diagnosis of fibromyalgia will also be 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 (*)])

Observation period

The observation period will start on the first day of treatment with Lyrica (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 Lyrica is judged unnecessary because of achievement of the purpose of treatment set at the start of treatment (e.g., cure of target diseases).

Planned survey period

Survey period : December 2012 to September 2016
Registration period : December 2012 to September 2015

Target sample size and rationale

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

The adverse reactions included in the major investigation items for Lyrica 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 Lyrica 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.

2.2. Study objective

The objectives of this survey are to obtain information about (1) the incidence of adverse reactions to Lyrica under actual use conditions, and (2) the factors which may affect the safety and efficacy of Lyrica 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 also be checked.*

3. Interim and final analyses

Interim analyses for periodical safety report will be regularly performed in this survey. Interim analyses will be performed only for items necessary for periodical safety report as specified in this plan. In addition, the final analysis for the application for reexamination will be performed. At the final analysis, all analyses specified in this plan will be performed.

4. Hypothesis and decision rule

4.1. Statistical hypothesis

Because this survey is not a confirmatory investigation, the testing should be considered as exploratory in nature. Unless otherwise specified, the 2-sided testing is performed with a significance level of 5%.

4.2. Statistical decision rule

Not applicable.

5. Analysis sets

5.1. Safety analysis set

The safety analysis set is the full analysis set that is as close to all patients treated with Lyrica as possible. More specifically, the safety analysis set is defined as the population of registered or reported patients, excluding those who meet any of the following conditions.

a. The survey form could not be collected at all (description in the report: “survey form not collected”).

b. There was a contract violation or deficiency (description in the report: “contract violation/deficiency”).

c. There was a registration violation (description in the report: “registration violation”).

d. Administration of Lyrica under survey has not been reported at all (description in the report: “no administration information”).

e. Information on adverse events has not been reported at all - no visits after the day of initial prescription (description in the report: “no adverse event information - no revisit”).

f. Information on adverse events has not been reported at all - adverse events not described (description in the report: “no adverse event information - not described”).

Detailed handling of patient inclusion in/exclusion from the analysis set should be in accordance with patient inclusion/exclusion criteria separately specified.

5.2. Efficacy analysis set

The efficacy analysis set is defined as the population excluding patients meeting any of the following conditions from the safety analysis set.

a. Efficacy evaluations have not been reported at all (description in the report: “no efficacy information”).

b. Non-target disease of the survey (description in the report: “non-target disease”)

Detailed handling of patient inclusion in/exclusion from the analysis set should be in accordance with patient inclusion/exclusion criteria separately specified.

5.3. Other analysis sets

Not applicable.

5.4. Subgroups

Subgroup analyses of safety and efficacy will be performed for the following patient demographics and other factors.

Subgroup analyses of safety will be performed for the following patient demographics and other factors.

- Hepatic impairment
- Renal impairment
- Children (<15 years), adults (≥15 to <65 years), elderly (≥65 years)
- Sex [male, female]
- Inpatient/outpatient status at the initial prescription [inpatient, outpatient]

- Body weight at the start of treatment (by sex) [<40 kg, ≥40 to <50 kg, ≥50 to <60 kg, ≥60 kg]
- Name of target disease [fibromyalgia, fibromyalgia and others, other]
- Hemodialysis [no, yes]
- Creatinine clearance [<15 mL/min, ≥15 to <30 mL/min, ≥30 to <60 mL/min, ≥60 mL/min]
- Past medical history [no, yes]
- Complications [no, yes]
- Prior medications [no, yes]
- Concomitant medications [no, yes]
- Non-medication therapies [no, yes]
- Timing of drug administration (at the start of treatment) [before meal, after meal, other]
- Daily dose (at the start of treatment) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤450 mg, >450 mg]
- Daily dose (maximum) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤450 mg, >450 mg]
- Pregnant and parturient women (pregnant)

Subgroup analyses of efficacy will be performed for the following patient demographics and other factors.

- Hepatic impairment
- Renal impairment
- Children (<15 years), adults (≥15 to <65 years), elderly (≥65 years)
- Sex [male, female]
- Inpatient/outpatient status at the initial prescription [inpatient, outpatient]
- Body weight at the start of treatment (by sex) [<40 kg, ≥40 to <50 kg, ≥50 to <60 kg, ≥60 kg]
- Name of target disease [fibromyalgia, fibromyalgia and others]
- Hemodialysis [no, yes]
- Creatinine clearance [<15 mL/min, ≥15 to <30 mL/min, ≥30 to <60 mL/min, ≥60 mL/min]
- Past medical history [no, yes]
- Complications [no, yes]
- Prior medications [no, yes]
- Concomitant medications [no, yes]
- Timing of drug administration (at the start of treatment) [before meal, after meal, other]
- Daily dose (at the start of treatment) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤450 mg, >450 mg]
- Daily dose (maximum) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤450 mg, >450 mg]

Furthermore, subgroups will be defined based on initial dose (information on administration of Lyrica: dose on Day 1), and exploratory analyses will be performed in the safety analysis set and efficacy analysis set.

- Initial dose <150 mg, 150 mg, >150 mg

6. Endpoints and covariates

6.1. Safety endpoints

- Adverse reactions: Adverse events determined to be related to Lyrica by the investigator or the sponsor
- Adverse events: All-causality adverse events
- Serious adverse reactions or adverse events: Adverse reactions or adverse events determined to be serious by the investigator or the sponsor
- Major investigation items:
  - Peripheral edema and edema-related events*
    *: Adverse events of the cardiovascular and respiratory systems will also be checked.
  - Dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury
  - Vision-related events

Events to be handled as major investigation items are defined as events of safety specification in the European risk management plan of Lyrica (important identified risk: peripheral edema and edema-related events; dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury; vision-related events).

- Accident-related events:

Accident-related events are defined as events coded to the MedDRA SMQ “accidents and injuries”. These events will be evaluated for adverse events.

- Pancreas-related events:

Pancreas-related events are defined as events coded to the MedDRA SMQ “acute pancreatitis (narrow scope),” those coded to the MedDRA HLGT “exocrine pancreas conditions” or the MedDRA HLT “pancreatic neoplasms malignant (excl islet cell and carcinoid)”, and those related to the laboratory test results of primary pancreatic parameters of serum amylase, lipase, and trypsin among those coded to the MedDRA SOC “Investigations”.

- Thyroidal function-related events:

Thyroidal function-related events are defined as events coded to the MedDRA SMQ "thyroid dysfunction".

- Change in appetite and activity-related events

Change in appetite and activity-related events are defined as events coded to the MedDRA PT "decreased activity", "decreased appetite", "increased appetite", or "hypokinesia".

- Euphoric mood-related events:

Euphoric mood-related events are defined as events coded to the MedDRA PT "euphoric mood".

- Suicide-related events:

Suicide-related events are defined as events coded to the MedDRA SMQ "suicide/self-injury". These events will also be evaluated for adverse events.

- Withdrawal symptom and rebound phenomenon-related events:

Withdrawal symptom and rebound phenomenon-related events are defined as events reported in patients with clinical findings at the completion of treatment of "yes" or events with the verbatim term of "withdrawal symptom and rebound phenomenon" reported.

Final identification of these events will be based on other background information available from patients experiencing the event.

- Skin disorder-related events:

Skin disorder-related events are defined as events coded to the MedDRA SOC "Skin and subcutaneous tissue disorders".

- Laboratory parameters:
  - Serum creatinine, serum amylase, free thyroxine (Free T4), serum total thyroxine (T4), thyroid-stimulating hormone (TSH), blood glucose (fasting), hemoglobin A1c (HbA1c), creatine kinase (CPK), triglyceride, LDL-cholesterol (LDL-Cho), prolactin
- Body weight

6.2. Efficacy endpoints

- Pain score: Patients are asked to rate their pain in the last 24 hours at the time of awakening on an 11-point scale from 0 (no pain) to 10 (worst possible pain).

- Sleep quality score: Patients are asked to rate the quality of their sleep in the last 24 hours at the time of awakening on an 11-point scale from 0 (best possible sleep) to 10 (worst possible sleep).

- Mental and physical questionnaire (Patient Health Questionnaire-9: PHQ-9): PHQ-9 is a self-completed questionnaire consisting of 9 questions and is used to evaluate depression-related symptoms.[1]
  Total score for answers to each question will be calculated as follows: 3 points for "almost every day", 2 points for "at least half of the week", 1 point for "a few days a week", and 0 point for "none".

- Health-related questionnaire (EQ-5D): EQ-5D is a comprehensive instrument for use as a measure of health-related QOL consisting of 5 questions (3 grades each).[2] Utility values are assigned to pairs of answers to the 5 questions based on the utility value conversion table of EQ-5D Japanese version (Appendix 1). No utility value is assigned if any of the questions is unanswered.

- Fibromyalgia activity scale (FAS-31): Widespread pain index (WPI) is used to assess the extent of chronic pain on a 20-point scale (0 to 19 points). For quantification of clinical disease based on clinical signs, severity of symptoms (symptom severity (SS)) and general physical symptoms are assessed on a 10-point scale (0 to 9 points) and on a 4-point scale (0 to 3 points), respectively. FAS-31 is calculated as the total score of WPI and SS.[3]

- Revised fibromyalgia questionnaire (JFIQR): JFIQR is the Japanese version of Fibromyalgia Impact Questionnaire (FIQ)[4] revised to make it more applicable to daily life. FIQ was developed as a questionnaire for comprehensive evaluation of the impact of disease on health in patients with fibromyalgia.
  JFIQR consists of questions on function (9 items), overall impact (2 items), and symptoms (10 items), assessed on an 11-point scale from 0 to 10. The total score of JFIQR ranges from 0 to 100, calculated by adding together the sum of function scores divided by 3 and the sum of overall impact scores plus the sum of symptoms score divided by 2.

- Patients' global impression of change (PGIC): Patients are asked to rate their impression relative to baseline on a 7-point scale from 1 (greatly improved) to 7 (greatly worsened).
  1 = greatly improved, 2 = improved, 3 = slightly improved, 4 = unchanged
  5 = slightly worsened, 6 = worsened, 7 = greatly worsened

- Clinical global impression of change (CGIC): Investigators rate their impression relative to baseline on a 7-point scale from 1 (greatly improved) to 7 (greatly worsened).
  1 = greatly improved, 2 = improved, 3 = slightly improved, 4 = unchanged
  5 = slightly worsened, 6 = worsened, 7 = greatly worsened

6.3. Other endpoints

- Number of days of absence from work (household chores, school, etc.) due to fibromyalgia in the last 4 weeks will be assessed at baseline and at Week 52 or the last observation time point.

6.4. Covariates

For safety and efficacy of Lyrica, no covariates or potential covariates are identified from clinical study data, etc. obtained to date.

7. Handling of missing data

If the seriousness/outcome of adverse events and action taken with Lyrica for the adverse events are missing, they will be handled as "unknown" at tabulation.

If laboratory parameters, body weight, and efficacy endpoints (excluding pain score and sleep quality score) are not measured within the acceptable window at each time point (Appendix 1), they will be handled as missing and will not be imputed.

If there is no data of pain score and sleep quality score, it will be handled as missing and will not be imputed in "Week 4", "Week 13", "Week 26" and "Week 52" assessments. If data is missing at Week 13 due to end (discontinuation) of treatment within 13 weeks, it will be imputed with the data obtained at the last time point post-dose in "Week 13 LOCF" assessment.

8. Statistical methods and statistical analyses

8.1. Statistical methods

8.1.1. Analysis of continuous data

Summary statistics (number of patients, mean, standard deviation, median, maximum, and minimum) will be calculated.

If a test is performed for comparison of before and after administration of Lyrica, a paired t-test will be used. If changes before and after administration of Lyrica (change = value after administration - value before administration) are compared between subgroups, the effect of the factor will be tested (P-value will be calculated) with an analysis of covariance model using the factor to be evaluated as a factor and the value before administration as a covariate, and the least squares mean, standard error, and 95% confidence interval of change will be calculated for each subgroup.

8.1.2. Analysis of categorical data

Frequency (e.g., number of patients) and its proportion (composition ratio) of each category will be calculated.

8.1.3. Analysis of binary data

Frequency and its proportion will be calculated. If the confidence interval of proportion is calculated, a 2-sided 95% confidence interval (exact method) will be calculated.

If the proportion is compared between subgroups, Fisher's exact test and Cochran-Armitage test (exact method) will be performed for the relationships with nominal scale data and ordinal scale data, respectively, and the risk ratio and risk difference with their 95% confidence intervals will be calculated.

8.2. Statistical analyses

8.2.1. General description of patients

- **Number of institutions and patients to be surveyed by establishment category**

Number of institutions and patients with their proportion by establishment category are to be calculated for the patients whose survey forms collected:

- National, public and private university hospitals
- National hospitals established by the Ministry of Health, Labour and Welfare
- Prefectural and municipal hospitals
- Public organizations
- Hospitals established by corporations and individuals not described above
- General practitioners and clinics

Additionally, mean, minimum, and maximum of the number of patients per institution will be calculated.

- **Patient disposition**

For registered patients, number of registered patients, patients whose survey form was collected, and patients included in the safety analysis set and efficacy analysis set will be tabulated. Also, number of patients whose survey form was not collected, patients excluded from safety analysis and efficacy analysis and number of patients by reason for exclusion will be tabulated.

- **Listing of discontinuations and dropouts**

Number and proportion of discontinued patients will be tabulated by timing of discontinuation (≤4 weeks, >4 to ≤13 weeks, >13 to ≤26 weeks, >26 to ≤52 weeks, and >52 weeks) in the safety analysis set. In addition, number and proportion of patients will be tabulated by reason for discontinuation.

- **Listing of excluded patients**

Listings of patients excluded from safety analysis and efficacy analysis, and reasons for exclusion will be prepared.

8.2.2. Patient demographics and treatment history

- **Patient demographics**

The following patient demographics will be tabulated in the safety analysis set and efficacy analysis set in accordance with Section 8.1.

- Sex [male, female]
- Age at the start of treatment (continuous data)
- Age category at the start of treatment [<15 years, ≥15 to <65 years, ≥65 years]
- Age category at the start of treatment [<65 years, ≥65 to <70 years, ≥70 to <75 years, ≥75 to <80 years, ≥80 to <85 years, ≥85 years]
- Inpatient/outpatient status at the initial prescription [inpatient, outpatient]
- Height at the start of treatment (by sex) (continuous data)
- Body weight at the start of treatment (by sex) (continuous data)
- Body weight category at the start of treatment (by sex) [<40 kg, ≥40 to <50 kg, ≥50 to <60 kg, ≥60 kg]
- Name of target disease [fibromyalgia, fibromyalgia and others, other]
- Duration of fibromyalgia (continuous data)
- Severity of fibromyalgia [mild, moderate, severe, unknown]
- Tender points based on 1990 ACR criteria for classification of fibromyalgia (continuous data)
- WPI and SS at the start of treatment (continuous data)
- Pain score (continuous data)
- Hepatic impairment [no, yes (mild, moderate, severe)]
- Renal impairment [no, yes (mild, moderate, severe)]
- Hemodialysis [no, yes]
- Creatinine clearance category [<15 mL/min, ≥15 to <30 mL/min, ≥30 to <60 mL/min, ≥60 mL/min]
- Hyperalgesia [no, yes]
- Number of days of absence from work (household chores, school, etc.) due to fibromyalgia in the last 4 weeks (continuous data)
- Past medical history [no, yes]
- Complications [no, yes]

The following number and proportion of patients will be tabulated by SOC and PT in the safety analysis set.

- Breakdown of past medical history
- Breakdown of complications

The following number and proportion of patients will be tabulated in the safety analysis set and efficacy analysis set.

- Presence or absence and breakdown of concomitant medications
- Presence or absence and breakdown of concomitant non-medication therapies
- Presence or absence and breakdown of prior medications

If patient demographics are tabulated by subgroup based on the initial dose specified in Section 5.4, the following will be tabulated in the safety analysis set and efficacy analysis set in accordance with Section 8.1.

- Age (continuous data)
- Age category [<15 years, ≥15 to <65 years, ≥65 years]
- Age category [<65 years, ≥65 to <70 years, ≥70 to <75 years, ≥75 to <80 years, ≥80 to <85 years, ≥85 years]
- Body weight at the start of treatment (by sex) (continuous data)
- Body weight category at the start of treatment (by sex) [<40 kg, ≥40 to <50 kg, ≥50 to <60 kg, ≥60 to <70 kg, ≥70 to <80 kg, ≥80 to <90 kg, ≥90 to <100 kg, ≥100 kg]
- Name of target disease [fibromyalgia, fibromyalgia and others, other]
- Duration of fibromyalgia (continuous data)
- Severity of fibromyalgia [mild, moderate, severe, unknown]
- Tender points based on 1990 ACR criteria for classification of fibromyalgia (continuous data)
- WPI and SS at the start of treatment (continuous data)
- Hepatic impairment [no, yes (mild, moderate, severe)]
- Renal impairment [no, yes (mild, moderate, severe)]
- Hemodialysis [no, yes]
- Creatinine clearance (continuous data)
- Creatinine clearance category [<15 mL/min, ≥15 to <30 mL/min, ≥30 to <60 mL/min, ≥60 mL/min]
- Past medical history [no, yes]
- Complications [no, yes]
- Past or present history of cardiovascular disorder[a] [no, yes]
- Past history of angioedema[b] [no, yes]

[a]: Past medical history or complications coded to the MedDRA SOC "Cardiac disorders" or "Vascular disorders"

[b]: Past medical history coded to the MedDRA HLT "angioedemas"

- Past medical history or complications (at the start of treatment): Peripheral edema and edema-related events[a] [no, yes]
- Past medical history or complications (at the start of treatment): Dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury[a] [no, yes]
- Past medical history or complications (at the start of treatment): Vision-related events[a] [no, yes]
- Concomitant medications (at the start of treatment) [no, yes]
- Concomitant use of analgesics[b] (at the start of treatment) [no, yes]
- Concomitant use of opioid analgesics[c] (at the start of treatment) [no, yes]
- Concomitant use of oxycodone or lorazepam[d] (at the start of treatment) [no, yes]
- Concomitant use of drugs causing angioedema[e] (at the start of treatment) [no, yes]
- Concomitant use of thiazolidines[f] (at the start of treatment) [no, yes]

- **Information on administration of Lyrica**

The following information on administration of Lyrica will be tabulated in the safety analysis set.

- Duration of administration [≤4 weeks, >4 to ≤13 weeks, >13 to ≤26 weeks, >26 to ≤52 weeks, >52 weeks]
- Timing of administration (at the start of treatment) [morning, noon, evening, bedtime, other]

[a]: The same definition as the major investigation items

[b]: The following analgesics will be considered as candidates and identified: drugs classified as "3 digits, 114 antipyretics, analgesics, and anti-inflammatory agents; 3 digits, 113 antiepileptics" in the drug name data file or drugs classified as "Standardised Drug Groupings (SDG), analgesia producing opioids; ATC 3rd level, N06A (ANTIDEPRESSANTS)" in the WHO-drug dictionary.

[c]: The following opioid analgesics will be considered as candidates and identified: drugs classified as "Standardised Drug Groupings (SDG), analgesia producing opioids" in the WHO-drug dictionary.

[d]: Drugs classified as "7 digits, 8119002 oxycodone hydrochloride hydrate or 1124022 lorazepam" in the drug name data file

[e]: The following drugs causing angioedema will be considered as candidates and identified: drugs classified as "4 digits, 6111 penicillins; 3 digits, 254 contraceptives" in the drug name data file or drugs classified as "Standardised Drug Groupings (SDG), non-steroidal anti-inflammatory drugs (NSAIDs); ACT 3rd level, C09A (ACE INHIBITORS, PLAIN), C09B (ACE INHIBITORS, COMBINATIONS), C09C (ANGIOTENSIN II ANTAGONISTS, PLAIN), C09D (ANGIOTENSIN II ANTAGONISTS, COMBINATIONS); ACT 3rd level, B01AD (Enzymes)" in the WHO-drug dictionary.

[f]: Drugs with non-proprietary name of pioglitazone in the drug name data file

- Timing of drug administration (at the start of treatment) [before meal, after meal, other]
- Daily dose (continuous data)
- Daily dose (at the start of treatment) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤450 mg, >450 mg]
- Daily dose (maximum) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤450 mg, >450 mg]
- Daily dose (final) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤450 mg, >450 mg]

Dosing period is from the day of initial dose in the survey to the day of last dose, including period of dose interruption. Daily dose (continuous data) will be calculated as the mean dose during the entire period in which Lyrica was actually administered to each patient excluding pro re nata (PRN) prescription, and the mean, standard deviation, and mode will be calculated in the safety analysis set.

8.2.3. Safety analysis

8.2.3.1. Adverse reactions

- **All adverse reactions**

Number and proportion of patients with adverse reactions will be tabulated by SOC and PT.

- **Serious adverse reactions**

Number and proportion of patients with serious adverse reactions will be tabulated by SOC and PT.

- **Details of adverse reactions**

Number and proportion of patients with adverse reactions will be tabulated by SOC and PT for each of the following items.

- Seriousness [Serious, non-serious]
- Expected/unexpected [expected, unexpected]
- Number of days to onset [≤4 weeks, >4 to ≤13 weeks, >13 to ≤26 weeks, >26 to ≤52 weeks, >52 weeks]
- Action taken [discontinuation, dose interruption or reduction, dose increase]
- Outcome [not recovered, recovered with sequelae, recovering, resolved/recovered, unknown]

If the same adverse reaction (the same PT) occurs more than once in the same patient, tabulation of the number of patients experiencing the adverse reactions will be handled as follows.

- Seriousness: Serious if both serious and non-serious reactions occurred.
- Expected/unexpected: Unexpected if both expected and unexpected reactions occurred.
- Number of days to onset: Number of days to onset of the first reaction
- Action taken: If more than one action were taken, select one action in the following order of priority: discontinuation, dose interruption or reduction, dose increase, none.
- Outcome: Outcome of the reaction lastly occurred in the patient.

- **Major investigation items**

Number and proportion of patients will be calculated for the following major investigation items.

- Peripheral edema and edema-related events*[a]
  *: Adverse events of the cardiovascular and respiratory systems will also be checked.
- Dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury
- Vision-related events

Furthermore, number and proportion of patients with major investigation items will be tabulated for each SOC and PT by seriousness, action taken and outcome.

For "peripheral edema and edema-related events", number and proportion of patients with events will be tabulated by presence or absence of weight increase. Two types of definitions of patients with weight increase are used: 1) those with "weight increased (MedDRA PT)" reported as an adverse reaction; 2) those with body weight increased by 7% or more from baseline at least once. Number and proportion of patients with adverse reactions will be tabulated for each SOC and PT by presence or absence of peripheral edema. In addition, number and proportion of patients with the following adverse reactions will be tabulated by presence or absence of peripheral edema to evaluate the relationship between peripheral edema and cardiovascular and respiratory events.

- Events coded to the MedDRA PT "arrhythmia", "atrial fibrillation", "cardiovascular disorder", "cardiac failure congestive" , "hypertension", "hypotension", "palpitations", "tachycardia", or "dyspnoea"
- Events coded to the MedDRA SOC "Cardiac disorders", "Vascular disorders", or "Respiratory, thoracic and mediastinal disorders"

[a]: Occurrence of cardiovascular and respiratory events will be examined in patients with peripheral edema and edema-related events.

For "dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury", number of days to onset will be tabulated using more specific categories (≤4 weeks [1 to 28 days], 1 to 7 days, 8 to 14 days, 15 to 21 days, 22 to 28 days; >4 weeks [≥29 days], >4 to ≤13 weeks, >13 weeks).

Moreover, the median number of days to onset will be tabulated for the following adverse reactions.

- Dizziness
- Somnolence
- Peripheral edema and edema-related events

- **Pancreas-related events, thyroidal function-related events, change in appetite and activity-related events, suicide-related events, withdrawal symptom and rebound phenomenon-related events, and skin disorder-related events**

Number and proportion of patients will be calculated for each event.

- **Patients with special background**

Number and proportion of patients with adverse reactions and serious adverse reactions will be calculated by SOC and PT in the following subgroups and other patients.

- Elderly patients
- Pediatric patients
- Patients with renal impairment
- Patients with hepatic impairment

Patients with renal impairment are defined as those with "Renal impairment: yes" or creatinine clearance of less than 60 mL/min.

- **Relationship between dosage and administration and development of adverse reactions**

In order to evaluate the relationship between dosage and administration and development of adverse reactions, number and proportion of patients with adverse reactions will be tabulated by SOC and PT for patients those with creatinine clearance and the initial daily dosage are ≥60 mL/min and 150 mg, respectively, and patients whose creatinine clearance and the initial daily dosage are ≥30 to <60 mL/min and 75 mg, respectively.

- **Relationship between prior and concomitant medications and development of adverse reactions**

In order to evaluate the relationship between the drug class of prior or concomitant medications and adverse reactions, number of patients with adverse reactions will be tabulated for each PT by drug class of prior or concomitant medications. However,

concomitant medications used after the initial onset of the event will be excluded from tabulation.

- **Occurrence of adverse reactions by inclusion in/exclusion from the safety analysis set**

A listing of adverse reactions in patients excluded from the safety analysis set will be prepared for patients whose survey form was collected. Moreover, number of patients with adverse reactions will be tabulated by SOC and PT.

8.2.3.2. Adverse events

- **All adverse events**

Number and proportion of patients with adverse events will be tabulated by SOC and PT.

- **Adverse events by serious/non-serious**

Number and proportion of patients with serious adverse events will be tabulated by SOC and PT. Non-serious adverse events will be tabulated in the same manner.

8.2.3.3. Other endpoints

- **Laboratory parameters**

Box-whisker plots of changes from baseline in laboratory parameters will be prepared at each time point as defined in Appendix 1.

- **Body weight**

Summary statistics specified in Section 8.1.1 will be calculated by time point as defined in Appendix 1 for measurements and their changes from baseline.

Number and proportion of patients with the following adverse reactions will be tabulated for patients whose body weight increased by 7% or more from baseline at least once and other patients.

- Abnormal glucose tolerance-related events: Events coded to the MedDRA HLGT "glucose metabolism disorders (incl diabetes mellitus)" or the MedDRA HLT "carbohydrate tolerance analyses (incl diabetes)"
- Dyslipidemia-related events: Events coded to the MedDRA HLGT "lipid metabolism disorders" or "lipid analyses"
- Events coded to the MedDRA PT "arrhythmia", "atrial fibrillation", "cardiovascular disorder", "cardiac failure congestive", "hypertension", "hypotension", "palpitations", "tachycardia", or "dyspnoea"
- Events coded to the MedDRA SOC "Cardiac disorders", "Vascular disorders", or "Respiratory, thoracic and mediastinal disorders"

8.2.3.4. Subgroup analysis

Number and proportion of patients with at least one adverse reaction will be tabulated by factor specified in Section 5.4. Tests specified in Section 8.1.3 will be performed to evaluate the relationship between patient demographics, etc. and development of adverse reactions. Furthermore, risk ratio and risk difference for the incidence of adverse reactions and their 95% confidence intervals will be calculated between subgroups.

In addition, number and proportion of patients with adverse reactions in each subgroup will be tabulated by SOC and PT for factors showing a significant difference by testing to evaluate the relationship between patient demographics, etc. and development of adverse reactions. Moreover, patient demographics, etc. (including breakdown of past medical history and complications, prior and concomitant medications) will be tabulated in each subgroup and number and proportion of patients with serious adverse reactions will be tabulated by SOC and PT in each subgroup as necessary.

8.2.3.5. Exploratory analysis

Number and proportion of patients with adverse reactions will be tabulated for each SOC and PT by subgroup based on the initial dose specified in Section 5.4.

Additional analyses of factors affecting safety may be performed as necessary. Results from exploratory analyses will be reported only if they provide important interpretation.

8.2.4. Efficacy analysis

8.2.4.1. Pain score

Summary statistics specified in Section 8.1.1 will be calculated for the pain score and its change from baseline at each time point as defined in Appendix 1, and test will be performed for comparison between before and after administration of Lyrica. Patients whose pain score at Week 13 LOCF decreased by at least 30% or at least 50% from baseline are defined as 30% or 50% responders, respectively. Then, number and proportion of responders will be calculated.

8.2.4.2. Sleep quality score

Summary statistics specified in Section 8.1.1 will be calculated for the sleep quality score and its change from baseline at each time point as defined in Appendix 1.

8.2.4.3. PHQ-9

Summary statistics specified in Section 8.1.1 will be calculated for the total score and its change from baseline[a] by time point as defined in Appendix 1.

8.2.4.4. EQ-5D

Summary statistics specified in Section 8.1.1 will be calculated for the utility value and its change from baseline[a] by time point as defined in Appendix 1.

8.2.4.5. FAS-31

Summary statistics specified in Section 8.1.1 will be calculated for the total score and its change from baseline[a] by time point as defined in Appendix 1.

8.2.4.6. JFIQR

Summary statistics specified in Section 8.1.1 will be calculated for the total score and its change from baseline[a] by time point as defined in Appendix 1.

8.2.4.7. PGIC

Number and proportion of patients will be calculated for each of 7-point scale.

8.2.4.8. CGIC

Number and proportion of patients will be calculated for each of 7-point scale.

8.2.4.9. Subgroup analysis

Subgroup analysis of the change from baseline in pain score at Week 52 (or at completion/discontinuation of treatment) will be performed by factor specified in Section 5.4. Summary statistics specified in Section 8.1.1 will be calculated, and test will be performed for comparison between subgroups based on the analysis of covariance model.

In addition, patient demographics, etc. (including breakdown of past medical history and complications, prior and concomitant medications) in each subgroup will be tabulated as necessary for factors showing a significant difference by testing to evaluate the relationship between patient demographics, etc. and efficacy.

[a] The protocol of this investigation specifies that "the proportion of effective patients relative to those evaluable for efficacy will be calculated" in the analysis of PHQ-9, EQ-5D, FAS-31, and JFIQR. However, no consensus has been reached on the definition of effective patients in these evaluations in terms of clinical or drug efficacy assessment. Therefore, changes from baseline will be analyzed.

8.2.4.10. Exploratory analysis

Summary statistics specified in Section 8.1.1 will be calculated for the change from baseline in pain score at Week 52 (or at completion/discontinuation of treatment) by drug class of concomitant medications for factors affecting efficacy.

In addition, the change in pain score at Week 13 (LOCF) will be calculated by subgroup based on the initial dose specified in Section 5.4, and patient demographics specified in Section 8.2.2 will be tabulated for patients with no improvement in the pain score(scores after treatment - before treatment ≥ 0).

Furthermore, additional analyses may be performed as necessary. Results from exploratory analyses will be reported only if they provide important interpretation.

8.2.5. Analyses of other endpoints

8.2.5.1. Number of days of absence from work (household chores, school, etc.) for fibromyalgia in the last 4 weeks

Summary statistics specified in Section 8.1.1 will be calculated for the number of days and its change from baseline at baseline and the last evaluation (Week 52 or the last observation time point).

9. Listings

The following listings will be prepared.

- Listing of patients
- Listing of patients with adverse events
- Listing of adverse reactions
- Listing of patients excluded from the safety analysis who experienced adverse reactions
- Listing of serious adverse reactions
- Listing of serious adverse events
- Listing of adverse reactions in patients with hepatic impairment
- Listing of adverse reactions in patients with renal impairment
- Listing of adverse reactions in the elderly
- Listing of adverse reactions (major investigation items)
- Listing of body weight and laboratory parameters
- Listing of patient-assessed pain score
- Listing of patient-assessed sleep quality score
- Listing of mental and physical questionnaire (PHQ-9)
- Listing of health-related questionnaire (EQ-5D)
- Listing of fibromyalgia activity scale (FAS-31)
- Listing of revised fibromyalgia questionnaire (JFIQR)

- Listing of patients' global impression of change (PGIC) and clinical global impression of change (CGIC)
- Listing of administration records
- Listing of initial dose and patient demographics, etc.

The following tables corresponding to appendix forms of periodical safety report will be prepared.

- Appendix Form 3 (Listing of patient summary)
- Appendix Form 2 (Summary of occurrence of adverse reactions and infections)
- Appendix Form 10 (Appendix Form 2-2) (Summary of occurrence of serious adverse events)

10. References

1. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16(9):606-13.

2. Ikegami N, Fukuhara S, Shimozuma K, et al. QOL evaluation handbook for clinical practice. Tokyo: Igaku Shoin; 2001: 45-9.

3. Japan College of Fibromyalgia Investigation. Diagnostic guidelines for fibromyalgia. Tokyo: Japan Medical Journal; 2013.

4. Bennett RM, Friend R, Jones KD, et al. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Res Ther. 2009; 11(4):R120.

11. Appendices

11.1. Appendix 1: Details of data extraction

A1.1 Data to be used for tabulation and analysis

Data collected after the safety evaluation date will not be used for tabulation and analysis specified in this plan. Data on efficacy endpoints (Section 6.2) will be used even if they are collected after the safety evaluation date.

A1.2 Definition of visit schedule

Visit schedule	Endpoint	Definition [acceptable window]
Start of treatment	Laboratory tests and body weight Efficacy endpoints	From 30 days before the first dose (date of start of treatment) in the survey to the date of start of treatment (Day 1)
After 4 weeks	Laboratory tests and body weight Efficacy endpoints	Day 29 [Day 2 to Day 60]
After 13 weeks	Laboratory tests and body weight Efficacy endpoints	Day 92 [Day 61 to Day 137]
After 13 weeks (LOCF)	Pain score and sleep quality score	Day 92 [Day 2 to Day 137]
After 26 weeks	Laboratory tests and body weight Efficacy endpoints	Day 183 [Day 138 to Day 273]
After 52 weeks	Laboratory tests and body weight Efficacy endpoints	Day 365 [Day 274 to Day 455]

If multiple data are collected within the acceptable window, the data whose date of evaluation is closer to the definition will be used for tabulation and analysis. If the difference from the definition is the same, the newer data will be used.

Efficacy evaluations performed within 14 days after the completion of the treatment period will be used.

A1.3 EQ-5D utility value conversion table

5D state	HRQOL	5D state	HRQOL	5D state	HRQOL	5D state	HRQOL	5D state	HRQOL
11111	1.000	12221	0.670	13331	0.419	22211	0.676	23321	0.459
11112	0.786	12222	0.608	13332	0.357	22212	0.613	23322	0.396
11113	0.736	12223	0.558	13333	0.307	22213	0.564	23323	0.346
11121	0.768	12231	0.557	21111	0.774	22221	0.596	23331	0.345
11122	0.705	12232	0.494	21112	0.711	22222	0.533	23332	0.282
11123	0.656	12233	0.444	21113	0.661	22223	0.483	23333	0.232
11131	0.654	12311	0.661	21121	0.693	22231	0.482	31111	0.430
11132	0.592	12312	0.599	21122	0.631	22232	0.419	31112	0.367
11133	0.542	12313	0.549	21123	0.581	22233	0.370	31113	0.318
11211	0.804	12321	0.581	21131	0.580	22311	0.587	31133	0.124
11212	0.742	12322	0.518	21132	0.517	22312	0.524	31211	0.386
11213	0.692	12323	0.469	21133	0.467	22313	0.474	31212	0.323
11221	0.724	12331	0.467	21211	0.730	22321	0.506	31121	0.350
11222	0.661	12332	0.405	21212	0.667	22322	0.444	31122	0.287
11223	0.612	12333	0.355	21213	0.617	22323	0.394	31123	0.237
11231	0.610	13111	0.747	21221	0.649	22331	0.393	31131	0.236
11232	0.548	13112	0.684	21222	0.587	22332	0.330	31132	0.173
11233	0.498	13113	0.634	21223	0.537	22333	0.280	31213	0.274
11311	0.715	13121	0.666	21231	0.536	23111	0.672	31221	0.306
11312	0.652	13122	0.604	21232	0.473	23112	0.609	31222	0.243
11313	0.603	13123	0.554	21233	0.423	23113	0.560	31223	0.193
11321	0.635	13131	0.553	21311	0.640	23121	0.592	31231	0.192
11322	0.572	13132	0.490	21312	0.578	23122	0.529	31232	0.129
11323	0.522	13133	0.440	21313	0.528	23123	0.479	31233	0.080
11331	0.521	13211	0.703	21321	0.560	23131	0.478	31311	0.297
11332	0.458	13212	0.640	21322	0.497	23132	0.415	31312	0.234
11333	0.409	13213	0.590	21323	0.448	23133	0.366	31313	0.184
12111	0.795	13221	0.622	21331	0.446	23211	0.628	31321	0.216
12112	0.732	13222	0.560	21332	0.384	23212	0.565	31322	0.154
12113	0.682	13223	0.510	21333	0.334	23213	0.516	31323	0.104
12121	0.714	13231	0.509	22111	0.720	23221	0.548	31331	0.103
12122	0.652	13232	0.446	22112	0.657	23222	0.485	31332	0.040
12123	0.602	13233	0.396	22113	0.608	23223	0.435	31333	-0.010
12131	0.601	13311	0.614	22121	0.640	23231	0.434	32111	0.376
12132	0.538	13312	0.551	22122	0.577	23232	0.371	32112	0.314
12133	0.488	13313	0.501	22123	0.527	23233	0.322	32113	0.264
12211	0.751	13321	0.533	22131	0.526	23311	0.539	32121	0.296
12212	0.688	13322	0.470	22132	0.463	23312	0.476	32122	0.233
12213	0.638	13323	0.421	22133	0.414	23313	0.426	32123	0.184

5D state	HRQOL	5D state	HRQOL
32131	0.182	33311	0.195
32132	0.120	33312	0.132
32133	0.070	33313	0.083
32211	0.332	33321	0.115
32212	0.270	33322	0.052
32213	0.220	33323	0.002
32221	0.252	33331	0.001
32222	0.189	33332	-0.062
32223	0.140	33333	-0.111
32231	0.138		
32232	0.076		
32233	0.026		
32311	0.243		
32312	0.180		
32313	0.131		
33122	0.185		
33123	0.136		
33131	0.134		
32321	0.163		
32322	0.100		
32323	0.050		
32331	0.049		
32332	-0.014		
32333	-0.063		
33111	0.328		
33112	0.266		
33113	0.216		
33121	0.248		
33132	0.072		
33133	0.022		
33211	0.284		
33212	0.222		
33213	0.172		
33221	0.204		
33222	0.141		
33223	0.092		
33231	0.090		
33232	0.028		
33233	-0.022		

11.2. Appendix 2: Details of statistical methods

A2.1 Subgroup analysis

Reference populations for calculation of risk ratio and risk difference in subgroup analyses of safety are shown below.

Factor	Category	Reference population	Safety/ Efficacy
Special population			
Hepatic impairment	Yes, No	None	Safety
Renal impairment	Yes, No	None	Safety
Age	Children (<15 years), adults (≥15 to <65 years), elderly (≥65 years)	Adults (≥15 to <65 years)	Safety
Patients demographics and others			
Sex	Male, female	Male	Safety
Age	<65 years, ≥65 to <70 years, ≥70 to <75 years, ≥75 to <80 years, ≥80 to <85 years, ≥85 years	<65 years	Safety
Inpatient/outpatient status at the initial prescription	Inpatient, outpatient	Outpatient	Safety
Body weight (by sex)	<40 kg, ≥40 to <50 kg, ≥50 to <60 kg, ≥60 kg	≥50 to <60 kg	Safety
Name of target disease	Fibromyalgia, fibromyalgia and others, other	Fibromyalgia	Safety
Hemodialysis	Yes, No	None	Safety
Creatinine clearance	<15 mL/min, ≥15 to <30 mL/min, ≥30 to <60 mL/min, ≥60 mL/min	≥60 mL/min	Safety
Past medical history	Yes, No	None	Safety
Complications	Yes, No	None	Safety
Prior medications	Yes, No	None	Safety
Concomitant medications	Yes, No	None	Safety
Non-medication therapies	Yes, No	None	Safety
Timing of administration (at the start of treatment)	Before meal, after meal, other	After meal	Safety
Daily dose (at the start of treatment)	≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤450 mg, >450 mg	>75 to ≤150 mg	Safety
Daily dose (maximum)	≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤450 mg, >450 mg	>150 to ≤300 mg	Safety