Non-Interventional Study Protocol

A0081261

Lyrica® Capsule Drug Use Investigation

Statistical Analysis Plan

Version: 8.0

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[redacted]

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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** **5.2. Efficacy analysis set** Patients with clinical evaluations data collected were additionally included in the efficacy analysis set. **6.1. Safety endpoints** Suicide-related events were added. **7. Handling of missing data** Modified to exclude efficacy evaluation from Appendix "Definition of visit schedule". LOCF (Week 13 [LOCF]) assessment was added for pain score and sleep interference score. **8.2.3.1. Adverse reactions** Tabulation of suicide-related events was added. **8.2.3.4. Exploratory analysis (safety)** Tabulation of the number and percentage of patients with adverse reactions by target disease (i.e., diagnosis of neuropathic pain) was added. **8.2.4.2. Pain score 8.2.4.3. Sleep interference score** Modified to exclude from Appendix "Definition of visit schedule". **8.2.4.7. Exploratory analysis (efficacy)** Analyses by target disease (i.e., diagnosis of neuropathic pain) were added for each assessment of efficacy other than clinical efficacy. **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 Handling of multiple observation data collected within the same visit window was additionally specified. **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. 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. Definition of weight-related endpoint was additionally specified. **8.2.3.1. Adverse reactions** Tabulation of major investigation item of peripheral edema and edema-related events was added. Tabulation of other safety endpoints was added. **Others** Description adjustment

Version/ Date/ Author(s)	Summary of Changes/Comments
4.0/ February 17, 2017/ PPD	**Status of survey: Ongoing** **6.1. Safety endpoints** Accident-related events and euphoric mood-related events were added as other safety endpoints. Evaluation of adverse events was added for suicide-related events. Laboratory parameters to be assessed as a population, and laboratory parameters to be assessed were added. **8.2.3.1. Adverse reactions** Tabulation of major investigation item of peripheral edema and edema-related events was added. Tabulation categories were added in the tabulation of major investigation item of dizziness, somnolence, loss of consciousness, syncope, and potential accidental for injury. 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. Laboratory parameters: Calculation of summary statistics was added. **8.2.3.4. Subgroup analysis** Calculation of summary statistics of laboratory parameters was added for patients whose target disease is painful diabetic neuropathy. **8.2.3.5. Exploratory analysis (safety)** The plan was reviewed taking into consideration the tabulation added in Section 8.2.3. after the preparation of the first version of SAP. **8.2.4.1. Clinical efficacy** Definition (equation) of response rate was added. **9. Listings** Listings were added. **A1.1 Data to be used for tabulation and analysis** Handling of efficacy-related data was additionally specified. **A1.2 Definition of visit schedule** Laboratory parameters were added to endpoints. **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. **8.1.1. Analysis of continuous data** Method of analysis of covariance 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 information on administration of Lyrica. **8.2.3.1. Adverse reactions** 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. **8.2.4.2. Pain score** Tabulation of responders was added. **8.2.4.6. Subgroup analysis (efficacy)** Analysis based on analysis of covariance model was added. **8.2.4.7. 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. Taking accumulated number of patients into consideration, scope of tabulation by target disease (i.e., diagnosis of neuropathic pain) was added to evaluate the relationship between prior and concomitant medications and development of adverse reactions. **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. **8.2.4.6. Subgroup analysis (efficacy)** Time points were specified for the analysis based on analysis of covariance model. **8.2.4.7. Exploratory analysis (efficacy)** Taking accumulated number of patients into consideration, scope of tabulation by target disease (i.e., diagnosis of neuropathic pain) was added. **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** **8.2.1. General description of patients** Tabulation of disease name of patients excluded from efficacy analysis because of non-target disease of the survey was added. **8.2.3.1. Adverse reactions** Tabulation of major investigation item of dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury by factor was added. 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. **8.2.4.6. 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** **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 drug use 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: Neuropathic pain*

○ *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. The dose may be adjusted depending on age and symptoms as*

appropriate, provided the daily dose may not exceed 600 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 not participating in any other survey or study of Lyrica*
- *Patients never having used Lyrica before the survey*

Observation period

The observation period will start on the first day of treatment with Lyrica (Day 1) and last until Week 13 (Day 91). However, in cases where treatment has been completed or discontinued before Week 13, observation will be continued until completion (discontinuation) of treatment, and follow-up will be made for one week (7 days) after completion (discontinuation) of treatment.
During this survey, 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), as a rule. In cases where treatment has been completed or discontinued, 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: *January 2011 to April 2017*
Registration period: *January 2011 to January 2017 (-91 days from the survey period)*

Target sample size and rationale

The target sample size is 3400 patients with neuropathic pain in total, including 3000 patients with peripheral neuropathic pain (1000 patients with postherpetic neuralgia, if possible, and 2000 patients with peripheral neuropathic pain of the types other than postherpetic neuralgia), and 400 patients with central neuropathic pain (300 patients with post-stroke pain, if possible, and other patients with pain following traumatic spinal cord injury and pain due to Parkinson's disease). For peripheral neuropathic pain, approximately 100 each of patients should be accumulated, if possible, for trigeminal neuralgia, peripheral entrapment neuropathy, iatrogenic neuropathy, neuropathy due to tumor-induced nerve compression or infiltration, posttraumatic pain, and chronic cauda equina syndrome.

The target sample size of 3400 patients with neuropathic pain is expected to have a 97% probability to detect adverse reactions occurring at the incidence of 0.1% or higher in at least 1 patient. Of the adverse reactions included in the major investigation items, vision-related events are anticipated to develop at the lowest incidence during the survey. In

clinical studies of Lyrica conducted in Japan and overseas, the lower bound of the 95% confidence interval for the incidence of this adverse reaction was 6.70% (incidence 7.40%, 380/5134 patients). If this adverse reaction develops at the same incidence as in these clinical studies, this reaction is expected to occur in 227 or more of 3400 patients. Since the safety and efficacy of Lyrica should be evaluated in patients with each type of neuropathic pain, enrollment of the following number of patients will be ensured; approximately 100 patients each, if possible, for trigeminal neuralgia, peripheral entrapment neuropathy, iatrogenic neuropathy, neuropathy due to tumor-induced nerve compression or infiltration, posttraumatic pain, and chronic cauda equina syndrome, approximately 300 patients for post-stroke pain, and a certain number of patients for pain following traumatic spinal cord injury and pain due to Parkinson's disease.

This sample size will also allow for adequate evaluation of the characteristics of other adverse reactions included in the major investigation items. The characteristics to be evaluated include time of onset and duration of adverse reactions, and these were also investigated in the clinical studies.

2.2. Study objective

The objective of this survey is to collect information on 1) adverse reactions that cannot be predicted from precautions for use (unknown adverse reactions), 2) the incidence of adverse reactions that will occur under actual use conditions, and 3) factors considered to affect safety, efficacy, etc. concerning the safety and efficacy of Lyrica in post-marketing routine clinical practice. At the same time, the necessity of conducting a special investigation or a post-marketing clinical study will be evaluated.
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 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)
- Age [<65 years, ≥65 to <70 years, ≥70 to <75 years, ≥75 to <80 years, ≥80 to <85 years, ≥85 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 (i.e., diagnosis of neuropathic pain) [by disease name]
- 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 ≤600 mg, >600 mg]
- Daily dose (maximum) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤600 mg, >600 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)
- Age [<65 years, ≥65 to <70 years, ≥70 to <75 years, ≥75 to <80 years, ≥80 to <85 years, ≥85 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 (i.e., diagnosis of neuropathic pain) [by disease name]
- 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 ≤600 mg, >600 mg]
- Daily dose (maximum) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤600 mg, >600 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".

- Body weight:

Events coded to the MedDRA PT "weight increased" are defined as events that should be investigated in the survey. Measurement values of body weight will also be evaluated.

- Laboratory parameters:

  – Serum creatinine, serum amylase, serum total thyroxine (T4), thyroid-stimulating hormone (TSH), fasting blood glucose, HbA1c

6.2. Efficacy endpoints

- Clinical efficacy: Efficacy of Lyrica at Week 13 will be assessed relative to baseline (including the day of start of treatment).

- 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 interference score: Patients are asked to rate their intensity of sleep interference in the last 24 hours at the time of awakening on an 11-point scale from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep [could not sleep because of pain]).

- 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

Not applicable.

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 body weight is not measured within the acceptable range at each time point (Appendix 1), it will be handled as missing and will not be imputed.

If there is no data of pain score and sleep interference score, it will be handled as missing and will not be imputed in "Week 4" and "Week 13" assessments. If data is missing at Week 13, 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, and >13 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. In addition, name of disease of patients excluded from efficacy analysis because of non-target disease of the survey will be tabulated by PT.

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 (i.e., diagnosis of neuropathic pain) [by disease name]
- Duration of target disease (i.e., diagnosis of neuropathic pain) (continuous data)
- Severity of target disease (i.e., diagnosis of neuropathic pain) [mild, moderate, severe]
- Pain score (continuous data)
- Name of underlying disease (i.e., primary disease of nerve damage that cause neuropathic pain) [by disease name]
- 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]
- 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 underlying disease
- 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 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]
- 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]
- Duration of target disease (i.e., diagnosis of neuropathic pain) (continuous data)
- Severity of target disease (i.e., diagnosis of neuropathic pain) [mild, moderate, severe]
- Name of underlying disease (i.e., primary disease of nerve damage that cause neuropathic pain) [by disease name]
- 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 medical history or complications of cardiovascular disorder[a] [no, yes]
- Past medical history of angioedema[b] [no, yes]
- Past medical history or complications (at the start of treatment): Peripheral edema and edema-related events[c] [no, yes]
- Past medical history or complications (at the start of treatment): Dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury[c] [no, yes]
- Past medical history or complications (at the start of treatment): Vision-related events[c] [no, yes]
- Concomitant medications (at the start of treatment) [no, yes]
- Concomitant use of analgesics[d] (at the start of treatment) [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"

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

[d]: 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.

- Concomitant use of opioid analgesics[a] (at the start of treatment) [no, yes]
- Concomitant use of oxycodone or lorazepam[b] (at the start of treatment) [no, yes]
- Concomitant use of drugs causing angioedema[c] (at the start of treatment) [no, yes]
- Concomitant use of thiazolidines[d] (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 weeks]
- Timing of administration (at the start of treatment) [morning, noon, evening, bedtime, other]
- 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 ≤600 mg, >600 mg]
- Daily dose (maximum) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤600 mg, >600 mg]
- Daily dose (final) [≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤600 mg, >600 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 dosage 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.

[a]: 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.

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

[c]: 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.

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

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 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"

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). In addition, number and proportion of patients with adverse reactions 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.

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

- Dizziness
- Somnolence

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

- 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 whose 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 target disease (i.e., diagnosis of neuropathic pain) and drug class of prior or concomitant medications. However, concomitant medications used after the initial onset of the event will be excluded from tabulation. For target disease, diseases with number of patients analyzed of approx.100 or more will be examined.

- **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. 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

- **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"

- **Laboratory parameters**

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

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.

Laboratory parameters will be tabulated as specified in Section 8.2.3.3 in patients whose target disease is painful diabetic neuropathy.

8.2.3.5. Exploratory analysis

Patient demographics (see Section 8.2.2) will be tabulated and number and proportion of patients with adverse reactions will be tabulated for each SOC and PT by target disease (i.e., diagnosis of neuropathic pain).

In addition, 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.

Furthermore, additional analyses 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. Clinical efficacy

Response rate (number of effective patients / [number of effective patients + number of ineffective patients]) and its 95% confidence interval will be calculated.

8.2.4.2. 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, 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.

8.2.4.3. Sleep interference score

Summary statistics specified in Section 8.1.1 will be calculated for the sleep interference score and its change from baseline at each time point, and test will be performed for comparison between before and after administration of Lyrica.

8.2.4.4. PGIC

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

8.2.4.5. CGIC

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

8.2.4.6. Subgroup analysis

Subgroup analysis of the response rate of clinical efficacy will be performed for each 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 clinical efficacy. Furthermore, test based on the analysis of covariance model specified in Section 8.1.1 will be performed to evaluate the relationship between patient demographics, etc. and change in pain score at Week 13 (or at administration/discontinuation).

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.

8.2.4.7. Exploratory analysis

Response rate of clinical efficacy will be calculated by target disease (i.e., diagnosis of neuropathic pain) and drug class of concomitant medications for factors affecting efficacy. Analyses specified in Sections 8.2.4.2 to 8.2.4.5 will be performed by target disease for each evaluation of efficacy other than clinical efficacy. For target disease, diseases with number of patients analyzed of approx.100 or more will be examined.

Response rate of clinical efficacy will be calculated by subgroup based on the initial dose specified in Section 5.4, and patients demographics specified in Section 8.2.2 will be tabulated for ineffective patients.

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

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 adverse reactions (accident-related events)
- Listing of body weight and laboratory parameters
- Listing of patient-assessed pain score
- Listing of patient-assessed sleep interference score
- 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. Appendices

10.1. 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 in 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	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	Day 29 [Day 2 to Day 60]
After 13 weeks	Laboratory tests and body weight	Day 92 [Day 61 to Day 137]

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.

10.2. 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 and efficacy are shown below.

Factor	Category	Reference population	Safety/ Efficacy
Special population			
Hepatic impairment	Yes, No	None	Safety, efficacy
Renal impairment	Yes, No	None	Safety, efficacy
Age	Children (<15 years), adults (≥15 to <65 years), elderly (≥65 years)	Adults (≥15 to <65 years)	Safety, efficacy
Patients demographics and others			
Sex	Male, female	Male	Safety, efficacy
Age	<65 years, ≥65 to <70 years, ≥70 to <75 years, ≥75 to <80 years, ≥80 to <85 years, ≥85 years	<65 years	Safety, efficacy
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, efficacy
Name of target disease [by disease name]		N/A	N/A
Hemodialysis	Yes, No	None	Safety, efficacy
Creatinine clearance	<15 mL/min, ≥15 to <30 mL/min, ≥30 to <60 mL/min, ≥60 mL/min	≥60 mL/min	Safety, efficacy
Past medical history	Yes, No	None	Safety
Complications	Yes, No	None	Safety
Prior medications	Yes, No	None	Safety, efficacy
Concomitant medications	Yes, No	None	Safety, efficacy
Non-medication therapies	Yes, No	None	Safety
Timing of administration (at the start of treatment)	Before meal, after meal, other	After meal	Safety, efficacy
Daily dose (at the start of treatment)	≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤600 mg, >600 mg	>75 to ≤150 mg	Safety, efficacy
Daily dose (maximum)	≤25 mg, >25 to ≤75 mg, >75 to ≤150 mg, >150 to ≤300 mg, >300 to ≤600 mg, >600 mg	>150 to ≤300 mg	Safety, efficacy