Non-Interventional Study Protocol
A0081262

Lyrica® Capsule Special Investigation
-Investigation on Long-term Use-

Statistical Analysis Plan

Version: 8.0

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TABLE OF CONTENTS

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 **5.2. 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". Specified that missing data will not be imputed for clinical efficacy. **8.2.3.1. Adverse reactions** Tabulation of suicide-related events was added. **8.2.4.2. Pain score 8.2.4.3. Sleep interference score 8.2.4.4. PGIC 8.2.4.5. CGIC** Modified to exclude from Appendix "Definition of visits". **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. **8.2.3.4. Subgroup analysis** Tabulation to evaluate the relationship between patient demographics, etc. and the development of adverse reactions associated with long-term use was added. **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. 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 of the relationship between dosage and administration and development of adverse reaction and the relationship between prior and concomitant 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. **8.2.4.1. Clinical efficacy** Definition (equation) of response rate was 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. **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** 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 daily dose (continuous data) and final daily dose was added as information on administration of Lyrica. **8.2.3.1. Adverse reactions** 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. **8.2.4.6. Subgroup analysis (efficacy)** Analysis of response rate of clinical efficacy was changed to analysis of pain score based on analysis of covariance model. **A.2.1 Subgroup analysis** Modification associated with changes in 8.2.4.6. Subgroup analysis. **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** 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. **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
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. **8.2.4.6. 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

Version/ Date/ Author(s)	Summary of Changes/Comments
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: 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 who are registered in the drug use investigation of Lyrica and are still on treatment with Lyrica after Week 13*

Observation period

The observation period of this survey will occur in succession to the 13-week observation period of the drug use investigation. It will start from Week 14 and last until Week 104 (Day 728 from the start of treatment counted as Day 1). However, in cases where treatment has been completed or discontinued before Week 104, observation will 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 Week 26, Week 52, Week 78, and Week 104 (including the last day of each 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).

During the observation period, the survey forms will be collected at Week 26, Week 52, Week 78, and Week 104.

Planned survey period

Survey period : April 2011 to April 2017
Registration period : April 2011 to August 2016

Target sample size and rationale

The target sample size is 310 patients who have been treated for at least 52 weeks and for 104 weeks at most.

Aiming at appropriate investigation of safety and efficacy of Lyrica during long-term use, the target sample size was set at 310, which is expected to have a 95% or higher probability to detect adverse reactions occurring at the incidence of 1% (0.97%) or higher in at least one patient.

A total of 310 patients with neuropathic pain who have been examined in the observation period of at least 52 weeks will be collected.

2.2. Study objective

The objective of this survey is to evaluate the safety and efficacy of long-term use of Lyrica in routine clinical practice.
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

For analysis of registered patients of the survey, data collected in the preceding drug use investigation and this survey will be used.

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]

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
- 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 104 (or at discontinuation/completion of treatment) 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 data on efficacy evaluation (clinical efficacy) at Week 104 (or at discontinuation/completion of treatment) are missing, the data will be handled as missing even when the results of evaluation at Week 26, 52, or 78 are available. The missing data will not be imputed.

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, >52 to ≤78 weeks, >78 to ≤104 weeks, and >104 weeks) in the safety analysis set. In addition, the 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 (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

- **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 to ≤78 weeks, >78 to ≤104 weeks, >104 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 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 to ≤78 weeks, >78 to ≤104 weeks, >104 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.

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

- **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. Furthermore, number and proportion of patients with at least one adverse reaction occurring (initial onset) at >13 to ≤52 weeks will be tabulated and tests

specified in Section 8.1.3 will be performed to evaluate the relationship between patient demographics, etc. and development of adverse reactions associated with long-term use. 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

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. 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 administration of Lyrica and at Week 104 (or at completion/discontinuation of treatment).

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 administration of Lyrica and at Week 104 (or at completion/discontinuation of treatment).

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 change from baseline in pain score at Week 104 (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.

8.2.4.7. Exploratory analysis

Additional analyses of factors affecting efficacy 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 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

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]
After 26 weeks	Laboratory tests and body weight	Day 183 [Day 138 to Day 273]
After 52 weeks	Laboratory tests and body weight	Day 365 [Day 274 to Day 455]
After 78 weeks	Laboratory tests and body weight	Day 547 [Day 456 to Day 637]
After 104 weeks	Laboratory tests and body weight	Day 729 [Day 638 to Day 819]

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 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 [by disease name]		N/A	N/A
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 ≤600 mg, >600 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 ≤600 mg, >600 mg	>150 to ≤300 mg	Safety