Non-Interventional Study Protocol
B3541003

LORA-PITA® Intravenous Injection 2 mg General Investigation

Statistical Analysis Plan

Version: 5.0

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1. REVISION FROM THE PREVIOUS VERSION

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
1.0 20-Mar-2019 PPD	First version
2.0 10-Jul-2020 PPD	Study status: Ongoing Section 5.1: It was added that patients who used LORA-PITA for a non-target disease will be included in the safety analysis set and will not be handled as patients with violation of registration. In order to ensure consistency with the description in the report, "- no description" was deleted from "description in the report, 'no adverse event information - no description.'" Section 8.1 3: A description was added stating that for subgroup analyses, if the number of patients is less than 10 in either or both categories for comparison, the number and proportion of patients will be calculated but risk ratio and its 95% confidence interval, and risk difference and its 95% confidence interval will not be calculated. Section 8.2 1.1: It was decided not to tabulate the number of study sites and number of study patients by establisher because they are not necessary for the report. Section 8.2.2.1: "Breakdown of non-drug therapies" was deleted because the information will be collected only for those used to treat adverse events and is not patient characteristic information. Section 8.2.3.4: A description was added stating that for subgroup analyses, if the number of patients is less than 10 in either or both categories for comparison, the number and proportion of patients will be calculated but risk ratio and its 95% confidence interval, and risk difference and its 95% confidence interval will not be calculated.

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
3.0 07-Feb-2022 PPD	Section 5.4: Reference groups for subgroup analyses of safety were presented. Categories of age at the initial onset of epilepsy were described. The age category of "combination of age category and presence/absence of diseases suggestive of treatment resistance" was specified to be the age at the initial onset of epilepsy. Sections 5.4 and 8.2.2.1: Medical history of epilepsy was added since it was considered meaningful in capturing refractory cases. The definition of epilepsy history was provided (Section 8.2.2.1). Sections 5.4 and 8.2.2.1: Details of epileptic seizure type classification (partial seizures, generalized seizures, unclassified epileptic seizures, neonatal seizures) were described. Section 8.2 2.1: It was specified to tabulate concomitant medications started during the observation period for more appropriate analysis. It was specified to tabulate both continuous and categorical data for age at the initial onset of epilepsy. Section 8.2 2.2: It was decided to delete the tabulation of administration time and tabulate the doses per kg for children for more appropriate analysis. Section 8.2.4: It was specified to present the number of responders by presence/absence of prophylactic administration as well because it was considered useful for discussion.
4.0 03-Feb-2023 PPD	Section 2.1: The study period and registration period were updated with changes in the study plan. Sections 5.4 and 8.2.2.1: For clarification purposes, the descriptions of concomitant use of drugs for status epilepticus, concomitant use of oral antiepileptic drugs and concomitant use of drugs that affect central nervous system depression (e.g., anesthetics, antidepressants, anxiolytics and hypnotics) were changed to treatment with drugs for status epilepticus (after the end of administration of LORA-PITA), treatment with oral antiepileptic drugs (after the end of administration of LORA-PITA) and treatment with drugs that affect central nervous system depression (e.g., anesthetics, antidepressants, anxiolytics and hypnotics) (concomitant use or after the end of administration of LORA-PITA), respectively. Section 8.2.2.1: For clarification purposes, the description "concomitant medications" in the breakdown of drugs for status epilepticus (prior medications, concomitant medications) and the breakdown of oral antiepileptic drugs (prior medications, concomitant medications) was changed to "after the end of administration of LORA-PITA," and the description "concomitant medications" in the breakdown of drugs that affect central nervous system depression (e.g., anesthetics, antidepressants, anxiolytics and hypnotics) was changed to "concomitant use or use after the end of administration of LORA-PITA." Section 9: It was decided to additionally prepare a list of contraindicated patients.

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
5.0 07-Nov-2023 PPD	Section 5.1: For 3, "other than use for non-target diseases" was deleted and "violation of registration" was provided for consistency with the description in the report. For 5, "no adverse event information - no description" was provided for consistency with the description in the report. Section 5.2: For 1, "efficacy not evaluable" was provided for consistency with the description in the report. Section 5.3: The populations of patients who provided consent for notification/publication of study results, the consented population (efficacy) and the consented population (safety), were set. Sections 5.4 and 8.2.2.1: For treatment with drugs for status epilepticus and treatment with oral antiepileptic drugs, "concomitant use or after the end of administration of LORA-PITA" was provided because some patients actually received these drugs in combination with LORA-PITA although it was not initially expected. Regarding concomitant use and after the end of administration of LORA-PITA, the definitions of concomitant use and after the end of administration of LORA-PITA were described in Section 5.4. Sections 5.4 and 8.2.2.1: Tabulation of patients using the usual dosage and administration specified in the package insert was added. Section 8.2: It was specified to perform analyses in the safety and efficacy analysis sets also in the consented population (safety) and the consented population (efficacy) in accordance with a list of forms to be separately prepared. Section 8.2.1.2: Patients who provided informed consent were also included. Section 8.2.2.1: It was specified to tabulate the breakdown of drugs for status epilepticus, oral antiepileptic drugs and drugs that affect central nervous system depression (e.g., anesthetics, antidepressants, anxiolytics and hypnotics) also by administration condition (concomitant use or after the end of administration of LORA-PITA). Section 8.2.3.2: Analysis of adverse events was divided into the analysis of serious adverse events and the analysis of non-serious adverse events. Section 8.2.3.4: Factors for tabulation of the number and proportion of patients with adverse reactions by SOC and PT were identified. Section 9: It was decided to additionally prepare a list of reasons for discontinuation.

2. INTRODUCTION

This Statistical Analysis Plan describes the statistical analysis plan for the general investigation of LORA-PITA® Intravenous Injection 2 mg (hereinafter referred to as LORA-PITA). In this plan, the texts quoted from the protocol are shown in *italics*.

2.1. Study design

LORA-PITA® Intravenous Injection 2 mg (nonproprietary name, lorazepam) is a benzodiazepine drug that has an anxiolytic effect, sedative effect and anticonvulsant effect. In Japan, its oral formulation (Wypax® Tablets 0.5 mg and 1.0 mg) was approved in 1977 for the indications "anxiety, tension and depression in nervous diseases" and "physical symptoms in psychosomatic disorders (autonomic imbalance and cardiac neurosis) as well as anxiety, tension and depression" and marketed. LORA-PITA® Intravenous Injection 2 mg (hereinafter referred to as LORA-PITA) is mentioned as a first-line drug in Western guidelines for the treatment of status epilepticus; however, because it was not approved in Japan, the Japan Epilepsy Society, Japanese Society of Child Neurology and Japan Psycho-Oncology Society submitted a development request in 2009. As a result of its review by the "Evaluation Committee on Unapproved or Off-label Drugs with High Medical Needs," LORA-PITA was judged to have high medical needs for the treatment of status epilepticus. Hence, the development of LORA-PITA was undertaken, and marketing approval was granted for the indication: "Status epilepticus."

A "LORA-PITA® Intravenous Injection 2 mg General Investigation" will be conducted to collect and evaluate the safety and efficacy data of LORA-PITA under actual use conditions in Japan.

This study is a multicenter cohort study conducted in patients receiving LORA-PITA, for which information required by the study will be recorded in case report forms (CRFs) based on patient data presented in medical records such as medical charts obtained in routine medical practice.

Planned study period
The planned period of this study is as follows:

Investigation period: 01 March 2019 to 02 June 2023

(The investigation period will be from the start of registration to the completion of the observation period of the last patient registered.)

Registration period: 01 March 2019 to 31 May 2023

(The registration period will be a period when the first dose of LORA-PITA is given. Registration will be terminated prior to the completion of the registration period if the target number of patients is reached.)

Study method

Fixed-point all patients surveillance system: This study will be conducted with fixed-point all patients surveillance system to enroll all patients who used LORA-PITA at specified contract sites (planned to be approximately 40 sites) after the conclusion of contracts and who meet the registration criteria (8.2.1.) for this study at the said sites.

Observation period

The observation period will be from the first dose of LORA-PITA to 24 hours after the end of the last dose. A follow-up period will be 24 hours after the end of the last dose, and if the follow-up period is less than 24 hours, such patients will be deemed as withdrawals.

The investigator shall make an inquiry on withdrawals to the patients or their families later than 24 hours after the end of the last dose by telephone or using other relevant means to the extent possible. After obtaining safety information up to 24 hours after the end of the last dose, the investigator shall evaluate adverse events (AEs) and input data.

Variables

This study will be conducted according to the following schedule of observation (Protocol Table 1).

Study size

Planned sample size

The target sample size is 120 patients who used LORA-PITA as a first-line drug (LORA-PITA is the first drug utilized for the target disease.). However, the maximum number of patients to be enrolled in the study is 200.

Rationale for sample size

Given that the efficacy rate for LORA-PITA is 55 to 80%, if 120 patients used this drug as the first-line treatment, both upper and lower limits of an estimated confidence interval are approximately 10% from the mean value. The statistical accuracy is considered sufficient to evaluate the efficacy of LORA-PITA. In this General Investigation, it is assumed that the proportion of patients who used lorazepam as the first-line treatment is about 60% in the registered patients, considering Key Opinion Leader's comments. However, if the actual number of patients who used lorazepam as the first-line treatment is small, even when 200 patients (established based on feasibility of the study) are registered, it can also be assumed that fewer than 120 patients used lorazepam as the first-line drug. However, even assuming that the proportion of patients who used lorazepam as the first-line treatment is extremely low at 30% (60 patients), if the efficacy rate of LORA-PITA is 55 to 80%, both upper and lower limits of an estimated confidence interval are about 15% from the mean value and it is possible to consider the efficacy of this drug. (Table 1)

Table 1. Clopper-Pearson two-sided 95% confidence interval (N=120 or 60) (Protocol Table 3 is re-presented)

Number of patients (N)	Assumption of efficacy (Proportion of efficacy/Patients who used lorazepam as the first line treatment)	95% confidence interval
120	55% (66/120)	45.7% - 64.1%
	60% (72/120)	50.7% - 68.8%
	65% (78/120)	55.8% - 73.5%
	70% (84/120)	61.0% - 78.0%
	75% (90/120)	66.3% - 82.5%
	80% (96/120)	71.7% - 86.7%
60	55% (33/60)	41.6% - 67.9%
	60% (36/60)	46.5% - 72.4%
	65% (39/60)	51.6% - 76.9%
	70% (42/60)	56.8% - 81.2%
	75% (45/60)	62.1% - 85.3%
	80% (48/60)	67.7% - 89.2%

2.2. Study objectives

This study intends to evaluate the safety and efficacy of LORA-PITA in patients who received this drug under actual use conditions after marketing.

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses for periodic safety reports will be performed periodically. At the time of interim analyses, only the analyses of the items necessary for periodic safety reports among the statistical analyses specified in this plan will be performed. In addition, the final analysis for the application for re-examination will be performed. All analyses specified in this plan will be performed at the time of the final analysis.

4. HYPOTHESES AND DECISION RULES

Since this study is not a confirmatory study, tests will be positioned as exploratory ones if conducted.

4.1. Statistical hypotheses

Since this study is not a confirmatory study, tests will be positioned as exploratory ones if conducted. Unless otherwise specified, the tests will be two-sided and the significance level will be 5%.

4.2. Statistical decision rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety analysis set

The safety analysis set is defined as the full analysis set that is as close as possible to all patients treated with LORA-PITA. Specifically, the safety analysis set is defined as a population of registered or reported patients excluding those who meet any of the following conditions:

1. The CRF could not be collected at all (description in the report, "CRF not collected")
2. There was a violation or flaw in the contract (description in the report, "contract violation/flaw")
3. There was a violation of registration (description in the report, "violation of registration")
4. Administration of the study drug has not been reported at all (description in the report, "no information on administration")
5. Information on adverse events has not been reported at all (description in the report, "no adverse event information - no description")

For details of each criterion, see the "Guidance for Criteria for Inclusion in Analysis Sets and Handling of Data in Drug Use Investigations."

5.2. Efficacy analysis set

The efficacy analysis set will consist of two populations, a patient population in which LORA-PITA is used as the first-line treatment with evaluable efficacy and a patient population in which efficacy can be evaluated, excluding patients who meet any of the following conditions in addition to the definition of the safety analysis set:

1. Efficacy evaluation has not been reported at all (description in the report, "efficacy not evaluable")
2. Disease not subject to the study (description in the report, “non-target disease”)
3. The dose was insufficient (description in the report, "insufficient administration")

5.3. Other analysis sets

Among the safety analysis set and the efficacy analysis set, the populations of patients who provided consent for notification/publication of study results are defined as the consented population (efficacy) and the consented population (safety), respectively.

5.4. Subgroups

Subgroup analyses of safety will be performed for the following patient characteristics. Concomitant use is defined as administration of drugs between the start time of administration of LORA-PITA and the end time of administration of LORA-PITA (final end time for multiple doses), and administration after the end of administration of LORA-PITA is defined as administration of drugs between the end time of administration of LORA-PITA (final end time for multiple doses) and 24 hours after the end of administration of LORA-PITA.

- Presence/absence of liver functional impairment (reference group: absent)
- Presence/absence of renal functional impairment (reference group: absent)
- Age [children (< 16 years), adults (≥ 16 years); also analyzed in subgroups of children (< 1 year, 1 to < 7 years, 7 to < 16 years) and adults (16 to < 65 years, ≥ 65 years)]
  [reference group: adults (≥ 16 years); 7 to < 16 years for pediatric subgroups and 16 to < 65 years for adult subgroups]
- Alcohol use (within 24 hours before the start of administration) [reference group: absent]
- Use of drugs that affect glucuronidation metabolism (probenecid and oral contraceptive steroids) (reference group: absent)
- Seizure subject to treatment with LORA-PITA, seizure symptom (status epilepticus/repetitive status epilepticus/others) [reference group: status epilepticus]
- Epileptic seizure type classification (partial seizures, generalized seizures, unclassified epileptic seizures, neonatal seizures) [reference group: partial seizures]

Subgroup analyses of safety will be performed for the following other factors:

- Pregnancy status (reference group: absent)
- Presence/absence of concurrent illness (reference group: absent)
- History of epilepsy (< 2 years, ≥ 2 years) [reference group: < 2 years]
- Presence/absence of treatment with drugs for status epilepticus (concomitant use or after the end of administration of LORA-PITA) (reference group: absent)
- Presence/absence of treatment with oral antiepileptic drugs (concomitant use or after the end of administration of LORA-PITA) (reference group: absent)
- Presence/absence of treatment with drugs that affect central nervous system depression (e.g., anesthetics, antidepressants, anxiolytics and hypnotics) (concomitant use or after the end of administration of LORA-PITA) (reference group: absent)
- Use of LORA-PITA as the first-line treatment (reference group: absent)
- Number of doses of LORA-PITA during the observation period (1, 2, > 2) [reference group: 1]

Patients possibly contraindicated in the package insert of LORA-PITA (hereinafter referred to as contraindicated patients) will be extracted and subgroup analyses of safety will be performed using separately specified criteria [reference group: not contraindicated].

Subgroup analyses of efficacy will be performed for the following patient characteristics:

- Age [children (< 16 years), adults (≥ 16 years); also analyzed in subgroups of children (< 1 year, 1 to < 7 years, 7 to < 16 years) and adults (16 to < 65 years, ≥ 65 years)]
- Seizure subject to treatment with LORA-PITA, seizure symptom (status epilepticus/repetitive status epilepticus)
- Epileptic seizure type classification (partial seizures, generalized seizures, unclassified epileptic seizures, neonatal seizures)
- Age at the initial onset of epilepsy (< 16 years, ≥ 16 to < 65 years, ≥ 65 years)
- Presence/absence of diseases suggestive of treatment resistance
- Combination of age at the initial onset of epilepsy and presence/absence of diseases suggestive of treatment resistance
- History of epilepsy (< 2 years, ≥ 2 years)
- Presence/absence of prior treatment with drugs for status epilepticus
- Presence/absence of prior treatment with oral antiepileptic drugs
- Presence/absence of prior treatment with drugs that affect central nervous system depression (e.g., anesthetics, antidepressants, anxiolytics and hypnotics)

- Patients who used the usual dosage and administration specified in the package insert [overall, children (< 16 years), adults (≥ 16 years); also analyzed in subgroups of children (< 1 year, 1 to < 7 years, 7 to < 16 years) and adults (16 to < 65 years, ≥ 65 years)]
  The usual adult initial and second doses are 4 mg, and the usual pediatric initial and second doses are 0.05 mg/kg (defined as ≥ 0.045 to < 0.055 mg/kg). Patients who received the third dose will not be included.

6. ENDPOINTS AND COVARIATES

6.1. Safety endpoints

- Adverse reactions: AEs for which the causal relationship was assessed as related by the physician
- AEs: All-causality AEs
- Serious adverse events (SAEs) or adverse reactions: AEs or adverse reactions assessed as serious by the physician
- Safety specifications: Respiratory depression, cardiac arrest, coma and paradoxical reactions (using the definitions provided in the RMP)

6.2. Efficacy endpoints

Epileptic seizures subject to treatment with LORA-PITA will be evaluated as efficacy evaluation.

- Definition of responders to the first or second administration of LORA-PITA: A responder is defined as a patient whose seizure resolved within 10 minutes after the first administration of LORA-PITA or the second administration (10 to 30 minutes after the first administration) and who does not require additional treatment with other drugs for the target disease within 30 minutes after the end of administration (excluding prophylactic administration) and has no recurrent seizure.
- Definition of responders within 10 minutes after the first administration of LORA-PITA: A responder is defined as a patient whose seizure resolved within 10 minutes after the first administration of LORA-PITA and who does not require additional treatment with other drugs for the target disease within 30 minutes after the end of administration (excluding prophylactic administration) and has no recurrent seizure.
- Definition of responders within 20 minutes after the first administration of LORA-PITA: A responder is defined as a patient whose seizure resolved within 20 minutes after the start of administration of LORA-PITA and who does not require additional treatment with other drugs for the target disease within 60 minutes after the start of administration (excluding prophylactic administration) and has no recurrent seizure.

6.3. Other endpoints

Not applicable.

6.4. Covariates

There are no covariates identified from previous clinical study data, etc. or potential covariates for the safety or efficacy of LORA-PITA.

7. HANDLING OF MISSING DATA

If the seriousness, treatment and outcome of an AE are missing, the data will be handled as "unknown" for tabulation.

Missing data will not be imputed for efficacy endpoints, vital signs and laboratory values.

The policy for handling uncleaned data is described below.

- Items of missing data: The items will be handled as missing (classification of categorical variables is "unknown") in both tabulation and listing.
- Items of inconsistent data: The items will be handled as missing in both tabulation and listing. However, a list of data handling will be prepared separately.

8. STATISTICAL METHODS AND STATISTICAL ANALYSIS

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.

8.1.2. Analysis of categorical data

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

8.1.3. Analysis of binary data

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

If the proportion is compared between subgroups, risk ratio, risk difference and their 95% confidence intervals will be calculated.

8.2. Statistical analysis

In accordance with a list of forms to be separately prepared, analyses in the safety analysis set will also be performed in the consented population (safety). Similarly, analyses in the efficacy analysis set will also be performed in the consented population (efficacy).

8.2.1. Overview of patients

8.2.1.1. Number of study sites and number of study patients by establisher

The number of study sites and number of study patients by establisher will not be tabulated.

8.2.1.2. Patient composition

In registered patients, the number of registered patients, patients who completed the study, patients included in safety analysis and patients included in efficacy analysis will be tabulated. In addition, the number of patients whose CRFs were not collected, patients excluded from safety analysis and patients excluded from efficacy analysis, and the number of patients by reason for exclusion will be tabulated. The same tabulation will be performed for patients who provided informed consent.

8.2.1.3. List of status of discontinuation/dropout

In the safety analysis set and the efficacy analysis set, the number and proportion of discontinued patients will be tabulated. In addition, the number and proportion of patients by reason for discontinuation will be tabulated.

8.2.1.4. List of excluded patients by patient

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

8.2.2. Patient characteristics and treatment history

8.2.2.1. Patient characteristics

In the safety analysis set and the efficacy analysis set, the following patient characteristics will be tabulated in accordance with Section 8.1. Epilepsy history will be calculated by "age at epileptic seizure – age at initial onset." Concomitant medications started during the observation period will be tabulated and listed.

- Sex [male, female]
- Age (continuous)
- Age [children (< 16 years), adults (≥ 16 years); also analyzed in subgroups of children (< 1 year, 1 to < 7 years, 7 to < 16 years) and adults (16 to < 65 years, ≥ 65 years)]
- Body weight (continuous)
- Pregnancy [absent, present] (only for women)
- Inpatient/outpatient status at initial prescription [inpatient, outpatient]
- Alcohol use (within 24 hours before the start of administration)
- Use of drugs that affect glucuronidation metabolism (probenecid and oral contraceptive steroids)

- Liver functional impairment [absent, present]
- Renal functional impairment [absent, present]
- Seizure subject to treatment with LORA-PITA, seizure symptom (status epilepticus/repetitive status epilepticus/others)
- Diseases suggestive of treatment resistance [absent, present]
- Epileptic seizure type classification [partial seizures, generalized seizures, unclassified epileptic seizures, neonatal seizures]
- Age at the initial onset of epilepsy (continuous)
- Age at the initial onset of epilepsy [< 16 years, 16 to < 65 years, ≥ 65 years]
- Past history [absent, present]
- Concurrent illness [absent, present]
- Use of LORA-PITA as the first-line treatment [absent, present]
- History of epilepsy [< 2 years, ≥ 2 years]
- Prior treatment with drugs for status epilepticus [absent, present]
- Prior treatment with oral antiepileptic drugs [absent, present]
- Prior treatment with drugs that affect central nervous system depression (e.g., anesthetics, antidepressants, anxiolytics and hypnotics) [absent, present]
- Treatment with drugs for status epilepticus (concomitant use or after the end of administration of LORA-PITA) [absent, present]
- Treatment with oral antiepileptic drugs (concomitant use or after the end of administration of LORA-PITA) [absent, present]
- Treatment with drugs that affect central nervous system depression (e.g., anesthetics, antidepressants, anxiolytics and hypnotics) (concomitant use or after the end of administration of LORA-PITA) [absent, present]
- Patients who used the usual dosage and administration specified in the package insert [overall, children (< 16 years), adults (≥ 16 years); also analyzed in subgroups of children (< 1 year, 1 to < 7 years, 7 to < 16 years) and adults (16 to < 65 years, ≥ 65 years)]
  The usual adult initial and second doses are 4 mg, and the usual pediatric initial and second doses are 0.05 mg/kg (defined as ≥ 0.045 to < 0.055 mg/kg). Patients who received the third dose will not be included.

In the safety analysis set, the number and proportion of patients will be tabulated by System Organ Class (SOC) and Preferred Term (PT) for the following:

- Breakdown of past history
- Breakdown of concurrent illness

In the safety analysis set and the efficacy analysis set, the number and proportion of patients will be tabulated by System Organ Class (SOC) and Preferred Term (PT) for the following:

- Breakdown of diseases considered to be the cause of status epilepticus
- Breakdown of diseases suggestive of treatment resistance

In the safety analysis set and the efficacy analysis set, the number and proportion of patients will be tabulated for the following:

- Breakdown of drugs for status epilepticus [prior medications, concomitant use or use after the end of administration of LORA-PITA (including breakdown by administration condition [concomitant use or after the end of administration of LORA-PITA])]
- Breakdown of oral antiepileptic drugs [prior medications, concomitant use or use after the end of administration of LORA-PITA (including breakdown by administration condition [concomitant use or after the end of administration of LORA-PITA])]
- Breakdown of drugs that affect central nervous system depression (e.g., anesthetics, antidepressants, anxiolytics and hypnotics) [prior medications, concomitant use or use after the end of administration of LORA-PITA (including breakdown by administration condition [concomitant use or after the end of administration of LORA-PITA])]

8.2.2.2. Status of administration of LORA-PITA

In the safety analysis set, the following status of administration of LORA-PITA will be tabulated:

- Number of doses
- Dose per administration
- Pediatric dose per administration (/kg)

8.2.3. Safety analysis

Safety endpoints assessed during the observation period will be tabulated. All events reported in this study will be included in the listing.

8.2.3.1. Adverse reactions

8.2.3.1.1. All adverse reactions

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

8.2.3.1.2. Serious adverse reactions

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

8.2.3.1.3. Details of adverse reactions

The 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]
- Treatment [no change in LORA-PITA dose, dose increase, dose reduction, interruption, discontinuation, not applicable]
- Outcome [not recovered, resolved/recovered, recovered with sequelae, recovering, fatal, unknown]

Multiple occurrences of the same adverse reaction (with the same PT) in the same patient will be handled as follows in the tabulation of the number of patients with events:

- Seriousness: If there are both serious and non-serious events, they will be regarded as serious.
- Treatment: If there are multiple types of action, one action will be adopted in the order of priority of discontinuation, interruption, dose reduction and others (no change in LORA-PITA dose, dose increase and not applicable).
- Outcome: The outcome of the last event will be used.

8.2.3.1.4. Safety specifications

For safety specifications, the number and proportion of patients with events will be tabulated.

8.2.3.1.5. Occurrence of adverse reactions by inclusion/exclusion in the safety analysis set

For patients whose CRFs were collected, a list of adverse reactions in patients excluded from the safety analysis set will be prepared. The number of patients with events will be tabulated by SOC and PT as necessary.

8.2.3.2. Adverse events

8.2.3.2.1. Serious adverse events

The number and proportion of patients with SAEs will be tabulated by SOC and PT.

8.2.3.2.2. Non-serious adverse events

The number and proportion of patients with non-serious AEs will be tabulated by SOC and PT. In this tabulation, the threshold of the incidence will be set as necessary, and only events with the incidence at or above the threshold will be tabulated.

8.2.3.3. Other endpoints

8.2.3.3.1. Vital signs

For blood pressure (systolic/diastolic), pulse rate and percutaneous arterial oxygen saturation (SpO2), the value before the start of administration or at the first administration of LORA-PITA (hereinafter referred to as the baseline value), final observation value and change from the baseline value to the final observation value will be summarized descriptively.

8.2.3.3.2. Laboratory values

For blood glucose and hematology (white blood cell count, red blood cell count, neutrophil, eosinophil, basophil, monocyte, lymphocyte and platelet count), baseline value, final observation value, and change from the baseline value to the final observation value will be summarized descriptively.

8.2.3.4. Subgroup analyses

The number and proportion of patients who experienced at least one adverse reaction will be tabulated by factor specified in Section 5.4. For children/adults (< 16 years, ≥ 16 years), children (< 1 year, 1 to < 7 years, 7 to < 16 years), adults (≥ 16 to < 65 years, ≥ 65 years), liver functional impairment (absent, present), renal functional impairment (absent, present), pregnancy (absent, present), concurrent illness (absent, present), treatment with drugs for status epilepticus (concomitant use or after the end of administration of LORA-PITA) [absent, present], treatment with oral antiepileptic drugs (after the end of administration of LORA-PITA) [absent, present] and treatment with drugs that affect central nervous system depression (e.g., anesthetics, antidepressants, anxiolytics and hypnotics) (concomitant use or after the end of administration of LORA-PITA) [absent, present], the number and proportion of patients with adverse reactions will be tabulated by SOC and PT. The risk ratio, risk difference and their 95% confidence intervals will be calculated. If the number of patients is less than 10 in either or both categories for comparison, the number and proportion of patients will be calculated but risk ratio and its 95% confidence interval, and risk difference and its 95% confidence interval will not be calculated.

8.2.3.5. Exploratory analyses

No exploratory analyses are planned, but additional analyses may be performed as necessary. Exploratory analyses will be reported only if results provide important interpretation.

8.2.4. Efficacy analysis

Two efficacy analysis sets will be specified: a population of patients evaluable for efficacy who used LORA-PITA as the first-line drug and a population of patients who are evaluable for efficacy.

In the abovementioned analysis sets, the following analyses will be carried out to assess the efficacy of LORA-PITA under actual use conditions in reference to Treiman DM's paper and the results from PECARN study and a Japanese Phase 3 study (B3541002) among four studies (including RAMPART study and PECARN study) corresponding to Class I according to the American Epilepsy Society (AES)

guidelines (2016) and the Japanese Phase 3 study (B3541002) listed in Table 2. The number of responders by presence or absence of prophylactic administration will also be tabulated.

- *Patients, whose seizure resolved within 10 minutes after the first administration of LORA-PITA or the second administration (10 to 30 minutes after the first administration) and who do not require additional treatment with other drugs for the target disease within 30 minutes after the end of administration (excluding prophylactic administration) and have no recurrent seizure, are defined as responders, and their proportion will be tabulated.*
- *Patients, whose seizure resolved within 10 minutes after the first administration of LORA-PITA and who do not require additional treatment with other drugs for the target disease within 30 minutes after the end of administration (excluding prophylactic administration) and have no recurrent seizure, are defined as responders, and their proportion will be tabulated.*
- *Patients, whose seizure resolved within 20 minutes after the start of administration of LORA-PITA and who do not require additional treatment with other drugs for the target disease within 60 minutes after the start of administration (excluding prophylactic administration) and have no recurrent seizure, are defined as responders, and their proportion will be tabulated.*

Table 2. Clinical studies to be used as references when examining the results of the drug use investigation (cited from Protocol Table 4)

Clinical study (year)	Design	Age group	Efficacy rate in the lorazepam injection group	95% confidence interval[b]	Efficacy criteria
Treiman DM (1998)[1]	Double-blind (LORA-PITA vs. diazepam/phenytoin vs. phenytoin vs. phenobarbital)	Adults (≥ 18 years)	64.9% (63[a]/97)	54.6% -74.4%	Resolution of seizure within 20 minutes after the start of administration without recurrence within 20 to 60 minutes after the start of administration
Alldredge BK (2001)[2]	Double-blind (LORA-PITA vs. diazepam vs. placebo)	Adults (≥ 18 years)	59.1% (39/66)	46.3% -71.0%	Resolution of seizure before arriving at the emergency outpatient unit
RAMPART (2012)[3]	Double-blind (LORA-PITA vs. midazolam intramuscular injection)	Adults and children (1 to 94 years)	63.4% (282/445)	58.7% - 67.9%	Resolution of seizure not requiring additional treatment and before arriving at the emergency outpatient unit
PECARN (2014)[4]	Double-blind (LORA-PITA vs. diazepam)	Children (3 months to 18 years)	72.9% (97/133)	64.5% - 80.3%	Resolution of seizure within 10 minutes after the start of administration without recurrence within 30 minutes after the start of administration
B3541002 (Japanese Phase 3 study, 2014-2016)	Open Open-label, uncontrolled (LORA-PITA)	Adults and children (0 to 49 years)	Primary endpoint 48.0% (12/25)	27.8% - 68.7%	Resolution of seizure within 10 minutes after the end of first administration of the investigational drug without recurrence within 30 minutes after the end of administration
			Key secondary endpoint 64.0% (16/25)	42.5% - 82.0%	Resolution of seizure within 10 minutes after the end of administration of the investigational drug [first administration or second administration (10 to 30 minutes after the first administration)] without recurrence within 30 minutes after the end of administration

1: Treiman DM, et al. N Engl J Med 1998; 339: 792–798.
2: Alldredge BK, et al. N Engl J Med 2001; 345: 631–637.
3: Silbergleit R, et al. N Engl J Med 2012; 366: 591–600.
4: Chamberlain JM, et al. JAMA 2014; 311: 1652-1660.
1 – 4: Corresponding to Class I of the American Epilepsy Society (AES) guidelines (Glauser T, et al. Epilepsy Curr. 2016; 16: 48-61.)
a: Estimated based on the efficacy rate and number of patients in the lorazepam injection group
b: Calculated using the Clopper-Pearson method based on the number of responders and patients

8.2.4.1. Subgroup analyses

Subgroup analyses of efficacy shown in Section 8.2.4 will be performed by factor specified in Section 5.4. In the analyses between subgroups, risk ratio, risk difference and their 95% confidence intervals will not be calculated.

8.2.4.2. Exploratory analyses

No exploratory analyses are planned, but additional analyses may be performed as necessary. Exploratory analyses will be reported only if results provide important interpretation.

9. LISTINGS

The following lists will be prepared.

- Patient listing
- List of administration status
- List of reasons for discontinuation
- List of efficacy endpoints
- List of patients with adverse events
- List of patients with adverse reactions
- List of patients with adverse reactions excluded from safety analysis
- List of contraindicated patients with adverse reactions
- List of patients with serious adverse reactions
- List of patients with serious adverse events
- List of patients with adverse reactions among patients with liver functional impairment
- Listing of patients with adverse reactions among patients with renal functional impairment
- List of pediatric patients (< 16 years) with adverse reactions
- List of elderly patients (≥ 65 years) with adverse reactions
- List of events corresponding to safety specifications (respiratory depression, cardiac arrest, coma and paradoxical reaction)
- List of laboratory values
- List of vital signs
- List of contraindicated patients

In addition, forms necessary for re-examination applications and periodic safety reports will be prepared in accordance with notifications.

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