(APPENDIX)

LORA-PITA® Intravenous Injection 2 mg General Investigation

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Pfizer Japan Inc.

STUDY INFORMATION

Title	LORA-PITA® Intravenous Injection 2 mg General Investigation
Protocol number	B3541003
Protocol version identifier	Ver. 5
Date	04 September 2023
Active substance	Lorazepam
Medicinal product	LORA-PITA® Intravenous Injection 2 mg
Research question and objectives	To evaluate the safety and efficacy of LORA-PITA® Intravenous Injection 2 mg in patients with status epilepticus who received this drug under actual use conditions after marketing.
Author	PPD PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
EDC	Electronic Data Capture
SpO_2	Oxygen Saturation by Pulse Oximetry
ILAE	International League Against Epilepsy

3. RESPONSIBLE PARTIES

The Japan Good Post-marketing Study Practice officer

4. AMENDMENTS AND UPDATES

Amendment number	Date	Type of amendment (Substantial or administrative)	Protocol section(s) changed	Summary of amendment(s)	Reason
Ver. 5	04 September 2023	Administrative amendment	9.3.	Descriptions edited	Change due to the revision of internal format
			12.	Contractor changed	Change of a contractor of EDC account management works
Ver. 4	18 November 2022	Substantial amendment	STUDY INFORMATION	Department name of the author changed	Organizational change
			5.,8.2.2., 8.6.1., 8.9., 9.4.	Items added and descriptions updated	Editing of descriptions
			6.	Ministerial ordinances and notices updated	Partial revision of ministerial ordinances
			8.6.6.	Fixed-point all patients confirmation method updated	Clearer description of the fixed-point all patients confirmation method
			10., 10.4.1., 10.4.3.	Japanese translation changed and descriptions edited	Change due to the revision of internal format
			Previous, 12.	Deleted (subsequent section numbers moved up)	Editing of descriptions due to notification of "Formulation and Publication of Risk Management Plan," dated 18 March

					2022
			12.	Scope of work contracted updated, and descriptions edited	Expansion of the scope of the contract
			16.1.	Name of the department for inquiries changed, and descriptions edited	Organizational change
			16.2.	Contact phone number for inquiries changed, and descriptions edited	Change of the contact phone number for inquiries
Ver. 3.1	07 June 2022	Administrative amendment	Cover page	Company logo changed	Change of the logo
Ver.3	10 May 2021	Substantial amendment	STUDY INFORMATION	The author changed	Change of the person in charge
			5.	The date of final study report changed	Change due to the extension of the planned study period
			8.2.2.	Study sites changed	Removal of "by specialists having knowledge in the area of the concerned disease" in order to ensure the target sample size
			5., 8.2.3.	The investigation period and registration period extended	Extension of the investigation period and registration period by 1 year and 3 months in order to ensure the target sample

					size
			8.6.6.	Fixed-point all patients registration method added	Correction of description omission
Ver. 2	10 October 2019	Administrative amendment	Cover, STUDY INFORMTATION 2, .8.3.8., 8.4., 8.6.1., 8.6.3., 8.7., 8.8., 11., 13.	Descriptions updated	Correction of errors and change/ editing for consistency with other sections
			8.3.6.	"Summary of the patient" added to section title	Consistency of language with Table 1. Variables and schedule of observation
			10.	Section added	Descriptions in a separate document included in this protocol
			13.	Scope of work added	Decision of a contractor of some works
			17.2.	E-mail address changed	Change of E-mail address of Medidata
Final	10 January 2019	NA	NA	NA	NA

5. MILESTONES

Milestone	Planned date
Start of data collection	01 March 2019
Start of data collection (date of registration of the first patient registered)	18 November 2019
End of data collection	02 June 2023
End of data collection (date of release of the database)	Around December 2023
Final study report	Around 2024

6. RATIONALE AND BACKGROUND

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 shall be conducted in strict compliance with the "MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 171, dated December 20, 2004), the "Enforcement of the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (PFSB Notification No. 1220008, dated December 20, 2004), "MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, Medical Devices, and Regenerative Medicine Products" (MHLW Ordinance No. 135, dated September 22, 2004), the "Enforcement of the MHLW Ordinance on the Standard for Post-marketing Safety Control of Medical Products, Quasi-medical Products, Cosmetics, Medical Devices, and Regenerative Medicine Products" (PFSB Notification No. 0812-4, dated August 12, 2014), "MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of Medical Products" (MHLW Ordinance No. 116, dated October 26, 2017), and "Announcement of the MHLW Ordinance to Partially Amend the MHLW Ordinance on the Standard for Post-marketing Studies and Clinical Trials of

Medical Products (Regarding the MHLW Ordinance on the Standard for Post-Marketing Studies and Clinical Trials of Medical Products)" (PSEHB Notification No. 1026-1, dated October 26, 2017).

7. RESEARCH QUESTION AND 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.

7.1. Safety Specifications

[Important identified risks]

- Respiratory depression
- Cardiac arrest
- Coma
- Paradoxical reaction

8. RESEARCH METHODS

8.1. Study design

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.

8.2. Setting

8.2.1. Registration criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study :

- Patients with status epilepticus who received LORA-PITA for the first time after the date when this drug was launched.

The indication, and dosage and administration of LORA-PITA are as mentioned below. Refer to the latest package insert of this drug when LORA-PITA is administered.

[Indication(s)] Status epilepticus

[Dosage and Administration] The usual dosage of lorazepam in adults is 4 mg administered intravenously. The drug should be given slowly with the administration rate at 2 mg/min as a guide. If necessary, 4 mg may be added but the dose should not exceed 8 mg as the sum of initial and additional doses.

The usual dosage of lorazepam in children aged 3 months or older is 0.05 mg/kg (up to 4 mg) administered intravenously. The drug should be given slowly with the administration rate at 2 mg/min as a guide. If necessary, 0.05 mg/kg may be added but the dose should not exceed 0.1 mg/kg as the sum of initial and additional doses.

8.2.2. Exclusion criteria

Not specified in this study.

8.2.3. Study sites

This study will be implemented at approximately 40 sites in total including the Department of Neurological Surgery, Department of Neurology and Emergency Room where emergency treatment is available and LORA-PITA is delivered.

8.2.4. 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.)

8.2.5. Study procedures

8.2.5.1. 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.

8.2.6. 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.

8.3. Variables

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

Table 1. Variables and schedule of observation

Variables \ Timing			At the time of registration (Registration form)	–	Observation period		
				Case report form			
				Before the start of LORA-PITA administration or at the first dose	After the first dose	After an additional dose (if applicable)	After the end of the last dose to 24 hours (Follow-up period)
Background	ID number		●	(●)*			
	Gender		●	(●)*			
	Birth year and month / age		●	(●)*			
	Day of the first dose of LORA-PITA		●	(●)*			
	Positioning of LORA-PITA for the target disease		●	(●)*			
	Eligibility		●				
	Body weight			●			
	Inpatient/outpatient status			●			
	History of drinking			●			
	Disease history (including identification of the causative disease and treatment-resistant disease)			●			
	Presence/absence of liver functional impairment and renal functional impairment			●			
	Information on the target disease (status epilepticus)	Seizure type classification		●			
		Date and time of onset		●			
		Seizure symptom		●			
	Age when the first epileptic episode occurred			●			
	Presence/absence of treatment with drugs affecting glucuronidation metabolism			●			
	Reason for using LORA-PITA			●			
	Pregnancy status (women only)			●			
Tests	Blood pressure, pulse rate			●	←		→
	Oxygen saturation by pulse oximetry			●	←		→
	Laboratory tests (Blood glucose/hematology)			●	←		→
LORA-PITA administration record (per administration)				●	●	(●)	
Concomitant therapy (Drug therapy/ Non-drug therapy)				←			→
Efficacy evaluation	Date and time of the resolution of seizure				←		→
	Information on recurrent seizure (only when applicable)					(●)	(●)
Adverse events**					←		→
Summary of the patient							●

* Some elements in the registration form are automatically reflected in the CRF.
** Adverse events: When the follow-up period is less than 24 hours, the investigator shall make an inquiry to the patients or their families by telephone or using other relevant means to the extent possible to assess safety up to 24 hours after the end of the last dose.

8.3.1. Patient characteristics

Enter the information at the start of administration of LORA-PITA in the registration form[1] (Information input in the registration form other than "eligibility" is automatically reflected in the CRF.)

- ID number
- Gender
- Birth year and month
- Day of the first dose of LORA-PITA
- Positioning of LORA-PITA for the target disease (whether or not this drug is the first drug administered)
- Eligibility

Input the following information prior to the start of administration of LORA-PITA in the CRF[2]:

- Body weight

  If body weight data prior to the start of administration are available, enter the body weight measured on a day nearest to the day of administration. For children, record body weight equivalent to the dose.

- Inpatient/outpatient status
- History of drinking (within 24 hours prior to the start of administration)
- Disease history (past history and concurrent illness)

  A disease by which a patient had been affected prior to LORA-PITA administration but cured at the time of LORA-PITA administration is deemed as "past history," and a disease by which a patient is affected at the time of LORA-PITA administration is "concurrent illness."

  For each disease history, enter whether or not a disease is likely to be the cause of status epilepticus or suggests treatment resistance.

- Presence/absence of liver functional impairment and renal functional impairment

  Liver functional impairment and renal functional impairment are not transient laboratory abnormalities but refer to an event that should be clinically noted and requires the follow-up.

- Reason for using LORA-PITA
- Seizure subject to treatment with LORA-PITA and seizure type classification

The type of a seizure subject to LORA-PITA treatment should be classified using the "Epileptic Seizure Type Classification" (Table 2) published in 1981 by the International League Against Epilepsy (ILAE).

- Seizure subject to treatment with LORA-PITA: Seizure symptom (status epilepticus/repetitive status epilepticus)
- Seizure subject to treatment with LORA-PITA: Time and date of onset
- Age when the first epileptic episode occurred
- Presence/absence of treatment with drugs (probenecid and oral contraceptive steroid) affecting glucuronidation metabolism
- Pregnancy status (women only)

Table 2. Epileptic Seizure Type Classification (ILAE, 1981 version)

Partial seizures	Generalized seizures
A. Simple partial seizures (consciousness not impaired) 1. With motor signs 2. With somatosensory or special sensory symptoms 3. With autonomic symptoms or signs 4. With psychic symptoms (Many of them are experienced as "complex partial seizures.")	A. 1. Absence seizures a. impairment of consciousness only b. with mild clonic components c. with atonic components d. with tonic components e. with automatisms f. with autonomic components (b through f may be used alone or in combination) 2. Atypical absence seizures a. changes in tone that are more pronounced than in A.1. b. onset and/or offset that is not abrupt
B. Complex partial seizures 1. Simple partial onset followed by impairment of consciousness a. simple partial onset b. motor onset 2. With impairment of consciousness at onset	B. Myoclonic seizures
C. Partial seizures evolving to secondarily generalized seizures	C. Clonic seizures

	D. Tonic seizures
	E. Tonic-clonic seizures
	F. Atonic seizures
Unclassified epileptic seizures	
Neonatal seizures rhythmic eye movements chewing swimming movements	

8.3.2. Administration of targeted drug

The following information will be recorded per administration for the status of LORA-PITA treatment:

- Dose
- Time and date of the start of administration
- Time and date of the end of administration

8.3.3. Drug therapy (premedication and concomitant medications)

8.3.3.1. Drugs for the treatment of status epilepticus

The presence or absence of the use of drugs corresponding to the following items during a period from 24 hours before the start of LORA-PITA administration to the completion of the observation period should be entered. If "present," the names of drugs used and their details (dose, time and date of the start of administration, time and date of the end of administration, and reason for administration) should be recorded.

- Diazepam injection
- Midazolam injection
- Phenobarbital injection
- Phenytoin injection
- Fosphenytoin injection
- Levetiracetam injection
- Thiopental injection
- Propofol injection
- Thiamylal injection
- Diazepam suppositories
- Chloral hydrate suppositories

- Phenobarbital suppositories
- Others

8.3.3.2. Oral antiepileptic drugs

The presence or absence of oral antiepileptic drugs used in combination during a period from 24 hours before the start of LORA-PITA administration to the completion of the observation period should be entered. If "present," the names of specific drugs used, and time and date of administration should be recorded.

8.3.3.3. Drugs affecting the inhibition of the central nervous system (e.g., anesthetics, antidepressants, anxiolytics and hypnotics)

The presence or absence of the use of drugs affecting the inhibition of the central nervous system during a period from 24 hours before the start of LORA-PITA administration to the completion of the observation period should be entered. If "present," the names of specific drugs used and their details (route of administration, time and date of the start of administration, and time and date of the end of administration) should be recorded.

8.3.3.4. Other concomitant medications (To be collected only for patients with AEs)

If an AE occurred after the start of LORA-PITA administration, the names of specific drugs used for the treatment of the AE should also be documented.

8.3.4. Non-drug therapy (To be collected only for patients with AEs)

If an AE occurred after the start of LORA-PITA administration, the names of specific non-drug therapies used for the treatment of the AE should also be recorded.

8.3.5. Tests/clinical laboratory tests

The results of the following tests performed from baseline (including the start time of administration) to the completion of the observation period should be recorded. An abnormal change in a laboratory value should also be documented in detail in the adverse event field, if it is clinically significant compared to the baseline value.

8.3.5.1. Vital signs

- Blood pressure (systolic and diastolic)
- Pulse rate
- Oxygen saturation by pulse oximetry (SpO_2)

8.3.5.2. Clinical laboratory tests

- Blood glucose
- Hematology (white blood cell count, red blood cell count, neutrophils, eosinophils, basophils, monocytes, lymphocytes and platelet count)

8.3.6. End-of-study (Discontinuation) record (Summary of the patient including Reason for discontinuation)

Enter the time and date of the completion of the observation period. If the follow-up period after the last administration of LORA-PITA is less than 24 hours, select and record only one of the following items that corresponds to the primary reason. If the AE is chosen, information should be also documented in the adverse event field:

- Completed
- AE
- Death
- Lost to follow-up
- Other

8.3.7. Evaluation of status epilepticus seizure (efficacy evaluation)

8.3.7.1. Time and date of resolution of seizure

Enter the time and date of the resolution of seizure treated with LORA-PITA. The resolution of seizure should be determined using the same criteria (visual inspection and electroencephalography) as those for the onset of seizure.

8.3.7.2. Time and date of recurrent seizure and time of resolution

If a seizure treated with LORA-PITA resolved once and then recurred (recurrent seizure) during the observation period, a seizure symptom (status epilepticus, repetitive status epilepticus or others), the time and date of seizure occurred, and the time and date of its resolution should be recorded for all recurrent seizers.

8.3.8. Adverse events

The occurrence of AEs from the start of LORA-PITA administration to the completion of the observation period should be confirmed, and the following information should be recorded.

Also, further investigation should be separately conducted, if deemed necessary by the Sponsor for patients who experienced a serious adverse reaction, an unexpected adverse reaction or other adverse reactions not listed in the package insert.

- Presence/absence of AE
- Name of AE
- Time and date of onset
- Time and date of resolution
- Intervention (presence/absence of a dose change and the details of treatment)
- Seriousness

- Outcome at the end of observation period and the date of outcome confirmed
- Causal relationship to LORA-PITA

If the AE is associated with an abnormal change in clinical laboratory values, the following information should also be recorded:

- Name of laboratory test
- Site reference value
- Unit
- Time and date of measurement
- Test results

8.4. Data sources

In this study, the investigators transcribe the necessary information from the medical record under daily medical practice in accordance with the protocol.

8.5. Study size

8.5.1. 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.

8.5.2. 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 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 used lorazepam as the first-line treatment is small, even when 200 patients (established based on feasibility of the study) are registered, it is also 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%, the two sides of the confidence interval width value are about 15% from the average value and it is possible to consider the efficacy of this drug (Table 3).

Table 3. Clopper-Pearson two-sided 95% confidence interval (N=120 or 60)

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%

8.6. Data management

8.6.1. Case report forms (CRFs)/ Electronic data record

As used in this protocol, the term CRF should be understood to refer to an electronic data record depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs must match those charts.

8.6.2. Record holding

The records related to this study should be retained at the study site until the End of Study Letter by Pfizer is received or during the period defined by the study site, whichever is longer.

8.6.3. Data collection method (EDC)

The data for this study will be entered in the CRF and confirmed by using the electronic system on the internet designed for collecting post-marketing survey data (Electronic Data Capture, EDC; hereinafter referred to as the EDC system).

8.6.4. Patient registration (EDC)

The investigator will enter registration items on the registration screen of EDC system and save the data. Patient registration will be performed immediately after the first dose of LORA-PITA is given to a patient meeting the registration criteria. If information in the registration form requires confirmation, the investigator may be requested to perform follow-up survey and respond to the query. Registration will be fixed after the query is resolved.

8.6.5. Points to consider for completion, revision, and submission of case report form (EDC)

8.6.5.1. Data entry

The investigator should confirm the survey items, and enter and save the data into EDC system based on information presented in medical charts.

8.6.5.2. Data revision

If entry omission or inconsistent data are identified after saving the data or upon receiving query from Sponsor on the contents of the CRF, the investigator will again confirm the contents of medical records, and as required, correct relevant sections and save the data.

8.6.5.3. Submission

After all data entry and revision are completed, CRFs should be signed electronically by the investigator in accordance with procedures specified by the Sponsor following re-confirmation of information entered in the CRFs.

8.6.6. Fixed-point all patients registration

1. The investigators at contract sites will regularly confirm that all patients who had been administered LORA-PITA have been registered, affix their signature or name and seal to the "All Patients Surveillance Confirmation Form," and submit the form to the site monitor. The form may be sent by e-mail or other means.

2. In the event of discovery of an unregistered patient, the registration of the corresponding patient should take place promptly.

8.7. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

8.7.1. Analysis for safety evaluation

The safety analysis set (SAS) consists of a full analysis set (FAS) that is as closer as possible to all patients who received LORA-PITA.

In the SAS, the occurrence and incidence (proportion of patients with AEs) of AEs during the observation period will be evaluated. Also, exploratory analyses will be, as necessary, performed such as evaluation of factors affecting safety.

8.7.2. Analysis for efficacy evaluation

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 4. In addition, exploratory analyses will be, as necessary, performed such as evaluation of factors affecting efficacy.

- 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 4. Clinical studies to be used as references when examining the results of the drug use investigation

Clinical study (year)	Design	Age group	Efficacy rate in the lorazepam injection group	95% confidence interval[b]	Efficacy criteria
Treiman DM (1998)[3]	Double-blind (LORA-PITA vs. diazepam/ phenytoin vs. phenytoin vs. phenobarbital)	Adults (≥ 18 years old)	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)[4]	Double-blind (LORA-PITA vs. diazepam vs. placebo)	Adults (≥ 18 years old)	59.1% (39/66)	46.3% - 71.0%	Resolution of seizure before arriving at the emergency outpatient unit
RAMPART (2012)[5]	Double-blind (LORA-PITA vs. midazolam intramuscular injection)	Adults and children (1 to 94 years old)	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)[6]	Double-blind (LORA-PITA vs. diazepam)	Children (3 months to 18 years old)	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 old)	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

3: Treiman DM, et al. N Engl J Med 1998; 339: 792-798.
4: Alldredge BK, et al. N Engl J Med 2001; 345: 631-637.
5: Silbergleit R, et al. N Engl J Med 2012; 366: 591-600.
6: Chamberlain JM, et al. JAMA 2014; 311: 1652-1660.
3 - 6: 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 numbers of responders and patients

8.8. Quality control

Prior to conducting the study, the site monitor will explain to the investigator about the contents of the protocol, etc. and ask the investigator for completion of CRFs based on medical charts.

8.9. Limitations of the research methods

There may be potential limitations in this study:

- Since no control group is included in the study, there is a limitation in determining whether or not a risk of developing AEs and adverse reactions increases with administration of LORA-PITA.
- Due consideration may not be given to confounding factors due to insufficient background information collected.
- Since this study collects the information described in medical charts, specified data may not be collected or may be missing.

8.10. Other aspects

Not applicable

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. The personal data of the patients will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, patient names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws (Personal Information Protection Act).

9.2. Patient Consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, or it is an information provision based on the law (even though that involves data subject to privacy laws according to applicable legal requirements), obtaining informed consent from patients by Pfizer is not required. Also, because the report of information or results collected in this study to the local regulatory authority or healthcare providers by Pfizer as needed is an information provision based on the law, obtaining informed consent from patients by Pfizer is not required.

In this study, Pfizer will collect information that cannot identify specific patients from the sites. The results of this study, which are prepared not to identify specific patients, may be reported to Pfizer Inc. or group companies, or regulatory authorities in other countries, as needed, or published as a presentation at academic conferences or a paper for the purpose of providing proper use information for this drug. If this information falls under personal information of the Personal Information Protection Act, these actions may not be based on the laws or regulations, and therefore, may correspond to provision to the third party and using the information for purposes other than business that require consent from the patient. Therefore, the study sites will obtain written or verbal consent from the patients to be included in this study so that Pfizer can use the results of this study to report to Pfizer Inc., group companies or regulatory authorities in other countries, or to present them at academic conferences or publish a paper, etc. Information regarding whether consent is obtained from patients or not is described in the CRF. The original of the written informed consent form should be retained by the investigator. In general, the investigator must obtain consent from a patient personally. However, if the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted or he or she is a minor, consent is obtained from legally acceptable representative or parent(s). In this case, every effort should be made to obtain the patient's assent as far as possible after obtaining consent from legally acceptable representative or parent(s) if a minor. If the study patient does not provide his or her own consent, the source documents must record the relationship of the person signing the consent and the patient (e.g., parent(s), spouse). If a minor registered in the study reaches adulthood during the study, the consent will be acquired as far as possible from the patient at the time of adulthood according to Japanese law.

At the time of obtaining informed consent, the investigator must use informed consent form and other materials and ensure that each study patient or his or her legally acceptable representative, or parent(s) if a minor, is fully informed about the information provided to Pfizer and the objectives of use and possible risks associated with consent.

9.3. Institutional Review Board (IRB)/Ethics Committee (EC)

In this study, review by the Institutional Review Board (IRB)/Ethics Committee (EC) is not required.

9.4. Ethical Conduct of the Study

This study will be conducted in compliance with the MHLW Ordinance in "6. RATIONALE AND BACKGROUND." Also, the study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS AND ADVERSE DRUG REACTIONS

10.1. Requirements for recording and reporting

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Non-Interventional Study Adverse Event Report Form (NIS AE Report Form) to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events."

Safety event	Recorded on the CRF	Reported on the NIS AE Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) Note: Any associated AE is reported together with the exposure scenario.

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (refer to section "Serious adverse events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to this drug**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient

death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

10.2. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of this drug and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to this drug, the SAE also must be reported to Pfizer Safety.

10.3. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to this drug, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that this drug caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether this drug caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that this drug did not cause the event, this should be clearly documented on the CRF and the NIS AE Report Form.

10.4. Definitions of safety events

10.4.1. Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;

- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

10.4.2. Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;

- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)

10.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) this drug, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to this drug (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to this drug prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

For exposure during pregnancy in studies of pregnant women, data on the exposure to the drug during pregnancy, are not reportable unless associated with serious or non-serious adverse events.

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed, with the exception of those studies conducted in pregnant women (as described in above), for which data on the exposure are not reportable unless associated with serious or non-serious adverse events.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with this drug, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AE Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to this drug in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AE Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Information collected in this study will be used for reporting purposes to report the Ministry of Health, Labour and Welfare (MHLW), Pharmaceuticals and Medical Devices Agency (PMDA), Pfizer Inc. which is the corporate parent of sponsor of this study, and the group companies, or regulatory agency in other countries. Also, it will be used for submitting application of re-examination (including Periodic Safety Update Report), re-evaluation, preparation of material for proper use information of LORA-PITA, publications and activities for information provision. In addition, Pfizer may disclose the study results to provide information for proper use, as needed, on www.clinicaltrials.gov

(ClinicalTrials.gov), as presentations at academic conferences, or as papers, etc.

Data obtained from the patients registered in this Study will be reported to the MHLW pursuant to the Pharmaceutical and Medical Device Act. In this case, the data may be publicly posted in the MHLW's "Pharmaceutical and Medical Device Safety Information" and "Pharmaceuticals and Medical Devices Information Website (http://www.info.pmda.go.jp)" as a listing of patients, which will include the names of drugs, adverse reactions, gender, age (increments of 10 years), and other relevant information. Furthermore, data collected may also be disclosed if the MHLW is required to disclose such information in accordance with the "Act on Access to Information Held by Administrative Organs" (Law No. 42 dated May 14, 1999); provided that in no event will the names of physicians, study sites, and other personal information be subject to such disclosure, nor will it be posted or disclosed.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

12. NAME, AND ADDRESS OF CONTRACTOR AS WELL AS SCOPE OF WORK CONTRACTED

Company name: Pfizer R&D Japan

Address: 3-22-7, Yoyogi, Shibuya-ku, Tokyo
Scope of work contracted: Planning of study, drafting of plan, implementation of study and monitoring, etc.

Company name: Medidata Solutions
Address: 2-7-2, Marunouchi, Chiyoda-ku, Tokyo
Scope of work contracted: Establishment, operation and maintenance of the EDC system, etc.

Company name: A2 Healthcare Corporation
Address: 1-4-1, Koishikawa, Bunkyo-ku, Tokyo
Scope of work contracted: EDC account management works

Company Name: EPS Corporation
Address: 2-23 Shimomiyabicho, Shinjuku-ku, Tokyo
Scope of work contracted: Registration, data management, statistical analysis etc. (works excluding the management of the post-marketing study)

13. ADDITIONAL MEASURES THAT MAY BE IMPLEMENTED BASED ON THE STUDY RESULTS AND CRITERIA FOR DETERMINATION OF THE INITIATION

Review the risk management plan including the following contents at the scheduled timing of milestones:

- Review the necessity for changing the contents of risk minimization activities for the current safety specifications.

- Review the necessity for changing the contents of this study plan including the presence or absence of new safety specifications (continuation of the study, implementation of additional study, etc.).

- Review the necessity for formulating risk minimization measures for new safety specifications.

14. SCHEDULED TIMING OF MILESTONES AND THEIR RATIONALES FOR EVALUATION OF STUDY IMPLEMENTATION STATUS AND RESULTS AND REPORTING TO THE PMDA

Safety review and reporting at the time of preparing the Periodic Safety Update Reports and completion of the study.

15. OTHER NECESSARY MATTERS

15.1. Amendment of the Study Protocol

Based on the new knowledge to be obtained according to the progress of this study, the need for amendment of the protocol will be examined and the Study Protocol will be amended if necessary. Also, the need for amendment of the Study Protocol will be examined and the protocol will be amended when the partial change in the dosage and administration or indication is approved during the reexamination period (except when the reexamination period is newly designated), etc.

15.2. Actions to be taken for any problem or issue

Revision of the package insert and conduct of a new post-marketing surveillance or new post-marketing clinical trial should be considered for the following cases: Any serious and unknown adverse reaction is suggested; a significant increase in the frequency of adverse reactions; any efficacy or safety concern compared to pre-approval; and/or rare adverse reaction is suggested.

16. CONTACT INFORMATION

16.1. Contact information for inquiries about the study

Name	PMS Affairs, Pfizer R&D Japan
Address	3-22-7, Yoyogi, Shibuya-ku, Tokyo 151-8589
Fax	03-5309-9186
E-mail address	LORAPITA_PMS@pfizer.com

16.2. Contact information for inquiries about the EDC system

Name	Medidata Helpdesk
Business hours	Weekdays: 9:00-20:00 (excluding Saturdays, Sundays, and holidays and year-end and New Year holidays)
Tel	PPD (Pfizer dedicated line)
E-mail address	japanhelpdesk@mdsol.com

17. REFERENCES

1. General Investigation: Registration Form

2. General Investigation: Case Report Form

3. Treiman DM, et al. N Engl J Med 1998; 339: 792–798.

4. Alldredge BK, et al. N Engl J Med 2001; 345: 631–637.

5. Silbergleit R, et al. N Engl J Med 2012; 366: 591–600.

6. Chamberlain JM, et al. JAMA 2014; 311: 1652-1660.

18. LIST OF TABLES

19. LIST OF FIGURES

Not applicable

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Not applicable

ANNEX 2. ADDITIONAL INFORMATION

1. General Investigation: Registration Form

2. General Investigation: Case Report Form

TRANSLATION RECORD (FOR POST-MARKETING SURVEILLANCE STUDY IN JAPAN)	10-Jan-2019

Document Type	実施要綱 v5.0		
Document Date (Original)	04 September 2023		
Program	B354	**Study**	B3541003
Original Language	日本語	**Site**	NA
Translation Language	英語	**Is a back translation required?**	NO

FULL TRANSLATION AND REVIEW INFORMATION

Translator Qualification Type	Translation vendor		
Translation Vendor	Honyaku Center Inc.		
Translator Name	Honyaku Center Inc.	**Date of Translation**	17 OCT 2023
Reviewer Name	PPD	**Date of Review**	09 NOV 2023