NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Observational study to investigate safety and effectiveness of lorlatinib as first line treatment for ALK-gene rearranged unresectable advanced/recurrent NSCLC patients in Japan clinical setting
Protocol number	[redacted]
Protocol version identifier	Version 6.0
Date	30 May 2025
EU Post Authorization Study (PAS) register number	EUPAS1000000117
Active substance	Lorlatinib (ATC code: L01ED05)
Medicinal product	Lorlatinib (LORBRENA®)
Research question and objectives	The overall objective is to describe special interested AEs with information regarding dose modification, and effectiveness of lorlatinib as first line treatment in clinical setting in Japan. The primary objectives are: 1. To characterize Adverse Events of special interests (AESIs: CNS AE, Hyperlipidemia, Edema) for patients treated with lorlatinib. 2. To investigate dose modifications, interruption, or discontinuation (if any), with related timing and reason. 3. To investigate time-to-treatment discontinuation (TTD) of lorlatinib.
Author	[redacted], PhD [redacted]

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AESI	Adverse Events of special interest
AEM	adverse event monitoring
ALK	anaplastic lymphoma kinase
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CSA	clinical study agreement
CT	computed tomography
DCF	Data Clarification Form
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
eCRF	electronic case report form
EDC	electronic data capture
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
HMA	Heads of Medicines Agencies
HR	hazard ratio
IC	Intracranial
ICD	informed consent document
IEC	independent ethics committee
IQR	interquartile range
IRB	institutional review board
MHLW	Ministry of Health, Labour and Welfare
NIS	non-interventional study
NR	not reached
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PR	partial response

Abbreviation	Definition
PS	performance status
RWD	real world data
SAP	statistical analysis plan
SD	stable disease
TKI	tyrosine kinase inhibitor
TNM	Tumor, Node and Metastasis
TTD	time-to-treatment discontinuation
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Name, Degree(s)	Job Title	Affiliation	Address
[redacted], PhD	[redacted]	[redacted]	[redacted]
[redacted], MD, PhD	[redacted]	[redacted]	[redacted]
[redacted], MSc	[redacted]	[redacted]	[redacted]

Implementation structure in this study including study sites and principal investigators will be prepared separately.

4. ABSTRACT

Title: Observational study to investigate safety and effectiveness of lorlatinib as first line treatment for ALK-gene rearranged unresectable advanced/recurrent NSCLC patients in Japanese clinical setting
Version (date) of protocol: Ver.6.0 (30 May 2025)
Name (affiliation) of main authors: [redacted] ([redacted])

Rationale and Background:
Lorlatinib is a selective, brain-penetrant ALK-TKI with potent activity against ALK and ROS1 fusions, including those harboring resistance mutations [1][2][3]. In Japan, lorlatinib was approved in 2018 for patients with ALK-positive advanced NSCLC whose cancer is resistant to ALK-TKIs. Subsequently, in 2021, lorlatinib was approved for the first line treatment of ALK -positive unresectable advanced/recurrent NSCLC based on the result of CROWN study [4]. In the phase 3, global, randomized CROWN study, lorlatinib significantly prolonged the progression-free survival (PFS) versus crizotinib in patients with untreated ALK-positive NSCLC (Hazard Ratio [HR]: 0.28, 95% Confidence Interval [CI]: 0.19-0.41, p<0.001). The most common AEs with lorlatinib were hyperlipidemia, edema, increased weight, peripheral neuropathy, and cognitive effects. It has been reported that most AEs are similar to those experienced with other targeted therapies; however, hyperlipidemia and CNS AEs (cognitive effect, mood effects, speech effects, and psychotic effects) are specific to lorlatinib treatment. Regarding CNS AEs, in the CROWN study, almost all patients who developed Grade 2 and 3 CNS AEs demonstrated recovery after dose reduction and/or interruption [6][7]. Despite the dose reduction/interruption due to AEs, the efficacy of lorlatinib does not seem to change [8].
The number of Japanese patients registered for the CROWN study was limited to 25 cases. Furthermore, in the post-marketing surveillance, only the factors affecting the AEs of the CNS and liver will be analyzed; the follow-up period and number of cases will be limited in the surveillance. Therefore, there is currently a lack of safety data for lorlatinib in clinical settings in Japan, including the outcomes of AEs, the real-world utilization of dose reduction/interruption, and the impact of AE management on the efficacy. In this study, we aim to elucidate the characteristics of CNS AE, hyperlipidemia, and edema. These specific AEs have been identified as areas of particular interest due to the relative unfamiliarity among Japanese physicians regarding their management. This focus aligns with the expressed needs of these physicians, thereby providing a tailored approach to addressing these medical challenges.

Research questions and objectives
The overall objective is to describe Adverse Events of special interests (AESIs: CNS AE, Hyperlipidemia, Edema) with information regarding dose modification, and effectiveness of lorlatinib as first line treatment in clinical setting in Japan.
The primary objectives are:
1. To characterize AESIs for patients treated with lorlatinib in first line setting.
2. To investigate dose modifications, interruption, or discontinuation (if any), with related timing and reason
3. To investigate time-to-treatment discontinuation (TTD) of lorlatinib.

The secondary objectives are:

4. To describe 1 year, 2 years and 3 years rate of real-world PFS/OS of patients on first line lorlatinib treatment.
5. To describe real-world ORR of patients on first line lorlatinib therapy.
6. To describe 1 year, 2 years and 3 years of real-world IC-PFS and IC-ORR of patients on first line lorlatinib therapy to investigate effectiveness of lorlatinib for CNS.
7. To describe subsequent treatment after permanent discontinuation of lorlatinib and the TTD of subsequent treatment.

Study Design

This is a multicenter, non-interventional study for patients with ALK-positive unresectable advanced/recurrent NSCLC treated with lorlatinib as first line treatment in Japan. The patients will be enrolled both retrospectively and prospectively based on the study initiation date. Retrospective cases will be identified when the patient has started lorlatinib as first line treatment before the study initiation date. Prospective cases will be identified when the patient will start lorlatinib as first line treatment after the study initiation date.

Data will be collected from eligible adults ALK-positive NSCLC treated with lorlatinib as first line treatment from the date of unresectable advanced/recurrent NSCLC diagnosis to the date of death, lost to follow-up, withdrawal of consent or end of study, whichever occurs first.

Population and setting

Inclusion criteria:

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

1. Adult (aged ≥18 years) with unresectable advanced/recurrent NSCLC
2. Confirmed ALK gene rearrangement by any validated test.
3. Initiating lorlatinib alone as first line treatment after confirmation of ALK-positive (i.e., no prior treatment with systemic therapy including ALK-TKI).
    i. Lorlatinib treatment has been initiated as first-line treatment at the medical institution conducting this study.
    ii. The following cases are not considered as prior systemic therapies:
        - Neoadjuvant/adjuvant therapy and chemo-radiation therapy (including maintenance therapy with immune checkpoint inhibitors) for NSCLC conducted more than 6 months before the diagnosis of unresectable advanced/recurrent NSCLC.
        - Systemic therapy for cancers other than NSCLC conducted more than 6 months before the diagnosis of unresectable advanced/recurrent NSCLC.
        - Hormonal therapy for cancers other than NSCLC.
4. Evaluated using computed tomography (CT), including the chest, and brain magnetic resonance imaging or CT for baseline assessment.
5. (For only patients who had already initiated lorlatinib before screening) Had at least one follow-up visit for evaluation of efficiency and safety after lorlatinib initiation.
    i. At least one record for medication, adverse events, or efficiency after lorlatinib initiation must be available.
6. Received lorlatinib after the marketing authorization date for first line treatment (25 November 2021) in Japan (for retrospective cases).

7. There is a signed and dated informed consent document (ICD)[*1] indicating that the research subject or their legally acceptable representative[*2] has been explained all matters related to this study. Furthermore, for patients who have transferred to another hospital, a written document is not mandatory, and registration through verbal[*3] informed consent is permitted.
(Considering the time and cost required to obtain informed consent, if obtaining informed consent from the research subject or their legally acceptable representative may hinder the implementation of this study, efforts should be made to obtain appropriate consent. Similarly, if it is difficult to obtain appropriate consent for the same reasons, registration through an opt-out method is permitted.)

*1: For prospective cases and retrospective cases who are followed up after the study initiation date, a signed and dated ICD is required, indicating that the patient (or their legally acceptable representative) has been explained all matters related to this study.

*2: The research subjects for whom informed consent is obtained from a legal representative or equivalent are as follows:
1) An adult who is objectively judged to lack the ability to give informed consent
2) Deceased individuals
†: The legally acceptable representative or equivalent should be someone who is considered capable of representing the interests and intentions of the research subject, selected with reference to the following conditions:
1) The research subject's spouse, parents, siblings, children, grandchildren, grandparents, cohabiting relatives, or those considered equivalent to these close relatives (excluding minors).
2) The research subject's agent (including a voluntary guardian who has been granted proxy rights).

††: This study aims to describe AESIs with information regarding dose modification and effectiveness of lorlatinib as first line treatment in clinical setting in Japan, therefore, patients who are/were treated with lorlatinib in routine clinical practice are the subjects of this study. Consequently, the research subjects include patients who lack the ability to give informed consent.

*3: If informed consent is obtained verbally, the method and content of the explanation, as well as the content of the consent received, should be recorded in the medical records.

Exclusion criteria:
No exclusion criteria are set in the study.

Variables
Demographic and patient characteristics of interest include age, sex, weight, height, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, comorbidities, date of unresectable advanced/recurrent NSCLC diagnosis, NSCLC histopathological subtype, NSCLC staging (based on Tumor, Node and Metastasis, TNM), presence and location of metastasis at baseline and NSCLC assessment.

Treatment variables of interest include lorlatinib dosing regimen (at initiation and after dose modification), duration of lorlatinib treatment, dates of dose modification, interruption or permanent discontinuation, concomitant treatment while on lorlatinib (surgery, radiotherapy, and chemotherapy), as well as subsequent treatment after permanent lorlatinib discontinuation. Outcomes of interest include real-world PFS, overall survival (OS), relative dose intensity, tumor response to lorlatinib and TTD for lorlatinib, TTD of subsequent treatment after lorlatinib, adverse events of special interest, adverse events including dose modification, interruption or discontinuation, interventions for adverse events.

Data sources:
Structured and unstructured data from patients' hospital medical records will be abstracted manually by a trained research associate. Data will subsequently be entered into a study-specific electronic data capture system (EDC) via a standardized electronic case report form (eCRF).

Study size:
The target number of study participants is 75, with a minimum of 60. As this is a descriptive case-series study with no a priori hypothesis, power calculation is not performed.

Data analysis:
All outcomes will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations.

Milestones

Milestone	Planned Date*
Completion of feasibility assessment	31 August 2024
Start of data collection/patient enrolment**	01 October 2024
End of patient enrolment	30 September 2026
End of data collection	Three years after the registration date of the 75th patient or 30 September 2029, whichever comes first.
Registration in the HMA-EMA Catalogues of RWD	31 August 2024
Final study report	31 August 2030

* Dates may change depending on study progress** This will be implemented after approval by the chief executive of the study site after approval by the institutional review board (IRB)/independent ethics committee (IEC).

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment (s)	Reason
Version 6.0	30 May 2025	Administrative	Section 4, 9.5	Removal of the mention of not limiting the number of registrations during the registration period	Given the current patient enrollment status, it is possible that the target of 75 patients could be reached before 30 September 2026. To accelerate the analysis, no additional patients will be registered once 75 patients have been enrolled.
		Administrative	Section 4,6,9.1., 9.1	Change of the end of data collection	Given the current patient enrollment status, it is possible that the target of 75 patients could be reached before 30 September 2026. To ensure a sufficient observation period while accelerating the start of the analysis, no additional patients will be registered once 75 patients have been enrolled.
		Administrative	Section 7	Addition of the spelled-out version of PASS	To clarify the definition
		Administrative	Section 9.3	Correction of variable item	To correct minor errors
Version 5.0	11 Februar y 2025	Administrative	Section 3	Change of the person in charge	To reflect organizational changes
		Substantial	Section 9.3	Clarification of the	To clarify the definition

				definition of Real-world IC-progression free survival	
Version 4.0	7 October 2024	Administrative	Section 3	Deletion of the person in charge	To reflect organizational changes
		Administrative	Section 4, 9.2.1.	Revision of the supplementary explanation for inclusion criterion 3	To clarify the supplementary explanation
		Administrative	Section 9.1	Change of the date for the second data cut-off	To reflect the change in the date for the second data cut-off
Version 3.0	25 July 2024	Administrative	Section 4	Deletion of variable item	To correct minor errors
		Administrative	Section 9.1	Clarification of the study contents	To correct minor errors
		Administrative	Section 10.1	Addition of the paper form for storing the personal data	To clarify the method of storing the personal data
		Administrative	Section 10.2	Clarification of the record retention period in the information provision and receipt part	To clarify the record retention period in the information provision and receipt part
		Administrative	Section 10.3	Addition of the explanation item and clarification of the method for informed consent document	To align accurately with the actual informed consent process

		Administrative	Section 10.5	Clarification of the process of institutional ethics committee	To clarify institutional ethics committee
Version 2.0	27 May 2024	Substantial	Section 9.2.1.	Clarification of the eligible subjects	To align the language regarding package insert in Japan
		Administrative	Section 6.	Update of Planned date of milestones and item name modification to HMA-EMA Catalogues of RWD	To update the dates according to current study timeline.
		Substantial	Section 9.1., 9.2.1., 9.6.3., 9.10.1., 10., 12., 14.	Clarification about the aim of the study and addition/correction for the contents (eg, patient consent, information provision, study disclosure) related to ethical guidelines	To ensure the alignment of ethical guidelines in Japan
		Substantial	Section 9.3.	Clarification of the definition of censoring regarding time to event analysis	To clarify the definition
		Administrative	Section 9.3.	Correction of variable	To correct minor errors

				timing and terminology	

6. MILESTONES

Milestone	Planned Date*
Completion of feasibility assessment	31 August 2024
Start of data collection/patient enrolment**	01 October 2024
End of patient enrolment	30 September 2026
End of data collection	Three years after the registration date of the 75th patient or 30 September 2029, whichever comes first.
Registration in the HMA-EMA Catalogues of RWD	31 August 2024
Final study report	31 August 2030

* Dates may change depending on study progress
** This will be implemented after approval by the chief executive of the study site after approval by the institutional review board (IRB)/independent ethics committee (IEC).

7. RATIONALE AND BACKGROUND

Lorlatinib is a selective, brain-penetrant ALK-TKI with potent activity against ALK and ROS1 fusions, including those harboring resistance mutations [1][2][3]. In Japan, lorlatinib was approved in 2018 for patients with ALK-positive advanced NSCLC whose cancer is resistant to ALK-TKIs. Subsequently, in 2021, lorlatinib was approved for the first line treatment of ALK -positive unresectable advanced/recurrent NSCLC based on the result of CROWN study [4]. In the phase 3, global, randomized CROWN study, lorlatinib significantly prolonged the progression-free survival (PFS) versus crizotinib in patients with untreated ALK-positive NSCLC (HR=0.28, 95% CI: 0.19-0.41, p<0.001). The response rate for intracranial lesions and median time to progression of intracranial lesions were 66% and not reached, respectively [4]. Moreover, in the 3-year follow-up of the CROWN study, lorlatinib continued to show superior overall and intracranial efficacy compared with crizotinib [5]. The most common AEs with lorlatinib were hyperlipidemia, edema, increased weight, peripheral neuropathy, and cognitive effects. Other AEs with varying frequencies (≥10%) include diarrhea, anemia, fatigue, hypertension, vision disorder, increased ALT and AST level, constipation, mood effects, nausea, and vomiting [4]. It has been reported that most AEs are similar to those experienced with other targeted therapies; however, hyperlipidemia and CNS AEs (cognitive effect, mood effects, speech effects, and psychotic effects) are specific to lorlatinib treatment. Regarding CNS AEs, in the CROWN study, almost all patients who developed Grade 2 and 3 CNS AEs demonstrated recovery after dose reduction and/or interruption [6][7]. Despite the dose reduction/interruption due to AEs, the efficacy of lorlatinib does not seem to change [8].

The number of Japanese patients registered for the CROWN study was limited to 25 cases. Furthermore, in the post-marketing surveillance, only the factors affecting the AEs of the CNS and liver will be analyzed; the follow-up period and number of cases will be limited in the surveillance. Therefore, there is currently a lack of safety data for lorlatinib in clinical settings in Japan, including the outcomes of AEs, the real-world utilization of dose reduction/interruption, and the impact of AE management on the efficacy. In this study, we aim to elucidate the characteristics of CNS AE,

hyperlipidemia, and edema. These specific AEs have been identified as areas of particular interest due to the relative unfamiliarity among Japanese physicians regarding their management. This focus aligns with the expressed needs of these physicians, thereby providing a tailored approach to addressing these medical challenges.
This noninterventional study is designated as a PASS (Post-Authorization Safety Study) and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective is to describe Adverse Events of special interests (AESIs: CNS AE, Hyperlipidemia, Edema) with information regarding dose modification, and effectiveness of lorlatinib as first line treatment in clinical setting in Japan.
The primary objectives are:

1. To characterize AESIs for patients treated with lorlatinib in first line setting.
2. To investigate dose modifications, interruption, or discontinuation (if any), with related timing and reason.
3. To investigate time-to-treatment discontinuation (TTD) of lorlatinib.

The secondary objectives are:

4. To describe 1 year, 2 years and 3 years rate of real-world PFS/OS of patients on first line lorlatinib treatment.
5. To describe real-world ORR of patients on first line lorlatinib therapy.
6. To describe 1 year, 2 years and 3 years of real-world IC-PFS and IC-ORR of patients on first line lorlatinib therapy to investigate effectiveness of lorlatinib for CNS.
7. To describe subsequent treatment after permanent discontinuation of lorlatinib and the TTD of the subsequent treatment.

9. RESEARCH METHODS

9.1. Study Design

This is a multicenter, non-interventional study for patients with ALK-positive unresectable advanced/recurrent NSCLC treated with lorlatinib as first line treatment in Japan. The patients will be enrolled both retrospectively and prospectively based on the study initiation date (**Figure 1**). This study aims to describe AESIs with information regarding dose modification and effectiveness of lorlatinib as first line treatment in clinical setting in Japan, therefore, patients who are/were treated with lorlatinib in routine clinical practice are the subjects of this study. Consequently, the research subjects include patients who lack the ability to give informed consent. As this is an observational real-world study, physicians will provide standard treatment based on their routine practices and in the best interests of the patients under their care.
All patients with a documented diagnosis of NSCLC and a record of lorlatinib use will be screened for study eligibility. Data will be collected from the date of unresectable advanced/recurrent NSCLC diagnosis to the study endpoint i.e., date of death, lost to follow-up, withdrawal of consent or end of study (observation period), whichever occurs first.

Case Definition:
We defined the “retrospective cases” and “prospective cases” based on the study initiation date (start of data collection date).

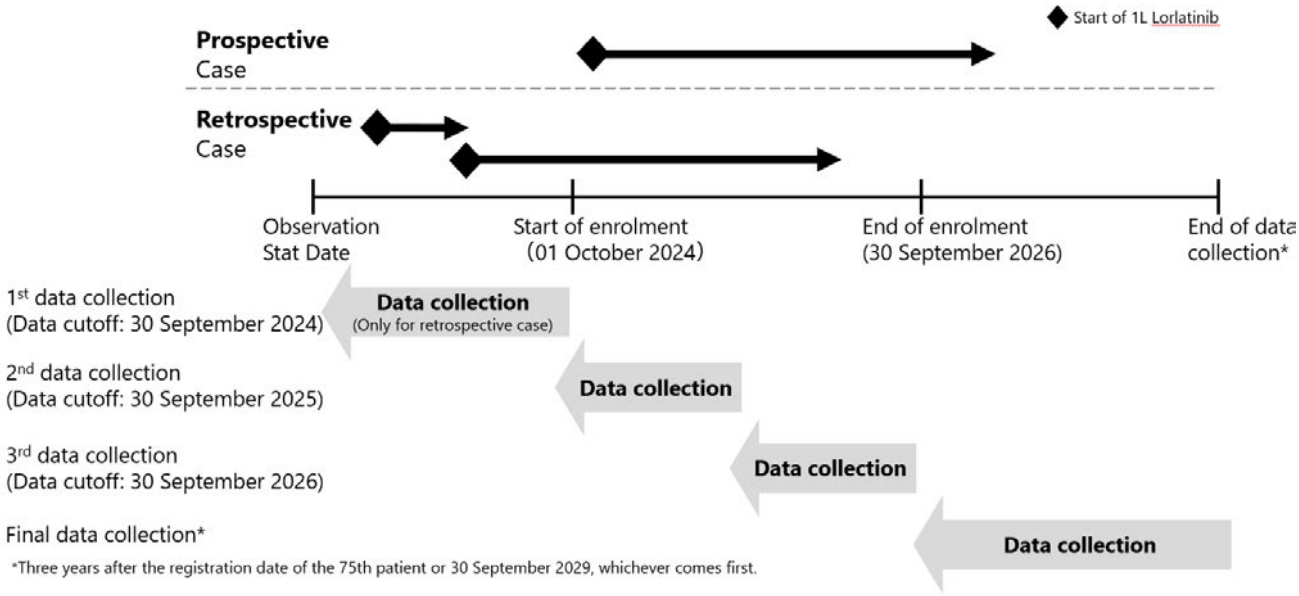
Retrospective cases will be identified when the patient has started lorlatinib as first line treatment before the study initiation date.
Prospective cases will be identified when the patient will start lorlatinib as first line treatment after the study initiation date. For prospective cases, the enrollment period will be from the study initiation date to 30 September 2026.

Data Collection:
Retrospective cases observed from 25 November 2021 to 30 September 2024 will be collected at the study initiation date and at the specified timing (based on each data cutoff) after the study initiation date.

Prospective cases observed on the study initiation date or later will be collected at the specified timing (based on each data cutoff) after the study initiation date.

Data cutoff date:
First data cut-off (only for retrospective cases): 30 September 2024
Second data cut-off: 30 September 2025
Third data cut-off: 30 September 2026
Final data cut-off: Three years after the registration date of the 75th patient or 30 September 2029, whichever comes first.

Figure 1. Schematic Diagram of the Study Design and Planned Data Collection Approaches

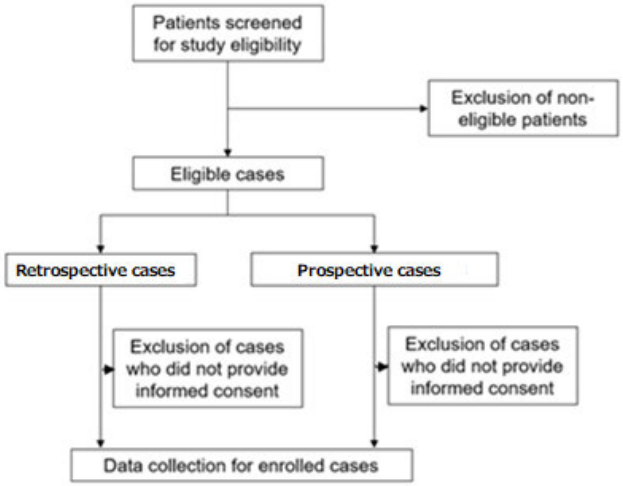


9.2. Setting

Approximately thirty cancer-treating hospitals in Japan are anticipated to be participating in this study. The total target number of patients will be 75, at least 60 for this study.
The inclusion and exclusion criteria for study participation are described in Sections 9.2.1 and 9.2.2.
Patient screening process for study eligibility will be performed as below (**Figure 2**):
All patients deemed eligible will be invited to participate in the study. An informed consent process will be carried out before data collection is conducted.

A standardized screening form will be used. Case screening will be performed by either the site investigator(s) or delegated clinical personnel assigned by the investigator. A screening log will be kept on all screened patients.

Figure 2. Diagram for Patient Screening Process



9.2.1. Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for inclusion in the study:
1. Adult (aged ≥18 years) with unresectable advanced/recurrent NSCLC
2. Confirmed ALK gene rearrangement by any validated test.
3. Initiating lorlatinib alone as first line treatment after confirmation of ALK-positive (i.e., no prior treatment with systemic therapy including ALK-TKI).
    i. Lorlatinib treatment has been initiated as first-line treatment at the medical institution conducting this study
    ii. The following cases are not considered as prior systemic therapies:
        - Neoadjuvant/adjuvant therapy and chemo-radiation therapy (including maintenance therapy with immune checkpoint inhibitors) for NSCLC conducted more than 6 months before the diagnosis of unresectable advanced/recurrent NSCLC.
        - Systemic therapy for cancers other than NSCLC conducted more than 6 months before the diagnosis of unresectable advanced/recurrent NSCLC.
        - Hormonal therapy for cancers other than NSCLC.

4. Evaluated using computed tomography (CT), including the chest, and brain magnetic resonance imaging or CT for baseline assessment.
5. (For only patients who had already initiated lorlatinib before screening) Had at least one follow-up visit for evaluation of efficiency and safety after lorlatinib initiation.
    i. At least one record for medication, adverse events, or efficiency after lorlatinib initiation must be available.
6. Treated lorlatinib after the marketing authorization date for first line treatment (25 November 2021) in Japan (for retrospective cases).
7. There is a signed and dated informed consent document (ICD)[*1] indicating that the research subject or their legally acceptable representative[*2] has been explained all matters related to this study. Furthermore, for patients who have transferred to another hospital, a written document is not mandatory, and registration through verbal[*3] informed consent is permitted. Please see the Section 10 for more details.
   (Considering the time and cost required to obtain informed consent, if obtaining informed consent from the research subject or their legally acceptable representative may hinder the implementation of this study, efforts should be made to obtain appropriate consent. Similarly, if it is difficult to obtain appropriate consent for the same reasons, registration through an opt-out method is permitted.)

   *1: For prospective cases and retrospective cases who are followed up after the study initiation date, a signed and dated ICD is required, indicating that the patient (or their legally acceptable representative) has been explained all matters related to this study.

   *2: The research subjects for whom informed consent is obtained from a legal representative or equivalent are as follows:
   1) An adult who is objectively judged to lack the ability to give informed consent
   2) Deceased individuals
   †: The legally acceptable representative or equivalent should be someone who is considered capable of representing the interests and intentions of the research subject, selected with reference to the following conditions:
   1) The research subject's spouse, parents, siblings, children, grandchildren, grandparents, cohabiting relatives, or those considered equivalent to these close relatives (excluding minors).
   2) The research subject's agent (including a voluntary guardian who has been granted proxy rights).

   ††: This study aims to describe AESIs with information regarding dose modification and effectiveness of lorlatinib as first line treatment in clinical setting in Japan, therefore, patients who are/were treated with lorlatinib in routine clinical practice are the subjects of this study. Consequently, the research subjects include patients who lack the ability to give informed consent.

   *3: If informed consent is obtained verbally, the method and content of the explanation, as well as the content of the consent received, should be recorded in the medical records.

9.2.2. Exclusion Criteria

No exclusion criteria are set in the study.

9.3. Variables

Variables for demographic and patients' characteristics, treatment and outcomes are presented in Table 1.

Table 1. Key Variables of Interest and Data Collection Timepoints

Role	Variable	Initiation of lorlatinib (Day 0[b])	Subsequent follow-up visits
Demographic and patient characteristic	Year and Month of birth (age)	X	
	Sex	X	
	Body weight	X	
	Height	X	
	Smoking status (current smoker, former smoker, never smoker)	X	
	Eastern Cooperative Oncology Group performance status[a]	X	
	Comorbidities	X	
	Date of unresectable advanced/recurrent non-small cell lung cancer (NSCLC) diagnosis	X	
	NSCLC histopathological subtype	X	
	Clinical NSCLC staging (based on Tumor, Node and Metastasis, TNM)	X	
	Presence and location of metastasis (including central nervous system, CNS)	X	
	History of surgery, chemotherapy, and radiotherapy	X	
Treatment	Lorlatinib (first line) initiation date	X	
	Lorlatinib initial dose and frequency	X	
	Lorlatinib dose modification date		X
	Lorlatinib dose and frequency after dose modification		X
	Lorlatinib dosing interruption and resumption date		X
	Lorlatinib permanent discontinuation date		X
	The subsequent treatment after lorlatinib discontinuation		X
	The subsequent treatment start and end dates		X

Role	Variable	Initiation of lorlatinib (Day 0[b])	Subsequent follow-up visits
	Lorlatinib duration, last dose and frequency (if not permanently discontinued)		X
	Concomitant treatment with lorlatinib (surgery, radiotherapy and chemotherapy)	X	X
Outcomes	Real-world progression-free survival (PFS)		X
	Real-world IC-progression-free survival (PFS)		X
	Overall survival (OS)		X
	Reasons (including adverse events) resulting in dosing modification, interruption or permanent discontinuation of lorlatinib		X
	Time-to-treatment failure (TTD) for lorlatinib		X
	Tumor response to lorlatinib		X
	IC-Tumor response to lorlatinib for the patients with brain metastasis at baseline		X
	Relative dose intensity		X
	Adverse Events of special interest (AESIs: CNS AE, Hyperlipidemia, Edema)		X
	Interventions for Adverse Events (including medications and physical therapy)		X

Abbreviations: CNS=central nervous system; NSCLC=non-small cell lung cancer; IC=intracranial; PFS= progression-free survival; TNM=Tumor Node Metastasis; TTD=time-to-treatment discontinuation.

a. See Annex 3A for more information.

b. Day 0 in this table represents the date of lorlatinib initiation

Operational definitions for outcomes are described in **Table 2**.

Table 2. Operational Definitions for Study Real-world Outcomes

Outcome	Definition
Real-world progression-free survival (PFS)	• Defined as the date from first line lorlatinib treatment start to disease progression during lorlatinib treatment, or death from any cause, whichever comes first. • If there are no clinical records of death or disease progression, they are censored at the date of initiation of the subsequent treatment, or at their last visit date for patients who does not receive the subsequent treatment. • Progression will be based on radiologist's interpretation of the imaging and/or clinician's note/interpretation taking into consideration all patient records including diagnostic and laboratory test results. • The date of NSCLC progression will be the earliest reported date of a progression event based on the available sources of documentation.
Real-world IC-progression-free survival (PFS)	• Defined as the date from first line lorlatinib treatment start to intracranial disease progression during lorlatinib treatment, surgery or radiotherapy for brain metastasis during lorlatinib treatment, or death from any cause, whichever comes first. • If there are no clinical records of death or disease progression, they are censored at the date of initiation of the subsequent treatment, or at their last visit date for patients who does not receive the subsequent treatment. • Progression will be based on radiologist's interpretation of the imaging and/or clinician's note/interpretation taking into consideration all patient records including diagnostic and laboratory test results. • The date of NSCLC progression will be the earliest reported date of a progression event based on the available sources of documentation.
Real-world IC-time to progression (TTP)	• Defined as the time from the initiation of first line lorlatinib to the date of the first documentation of objective progression of intracranial disease during lorlatinib treatment, based on either new brain metastases or progression of existing brain metastases. • If there are no clinical records of intracranial disease progression, the date of censoring is based on death, the subsequent treatment, or their last visit date, whichever comes first. • Progression of intracranial disease will be based on radiologist's interpretation of the imaging and/or clinician's note/interpretation taking into consideration all patient records including diagnostic and laboratory test results.

Outcome	Definition
	• The date of progression of intracranial disease will be the earliest reported date of a progression event based on the available sources of documentation.
Adverse events resulting in dose modification, dosing interruption or permanent discontinuation of lorlatinib	• Defined as the presence of at least one of the below clinical events and documented evidence of lorlatinib dose modification, dosing interruption or permanent discontinuation: · CNS AE* · Hyperlipidemia · Edema · Other adverse events related to lorlatinib *CNS AE is classified into five categories: cognitive disorder, speech disorder, mood disorder, hallucination, and unknown. • Dose modification is defined as any dose change (increase or decrease) from prior lorlatinib treatment regimen. • Dosing interruption is defined as lorlatinib treatment being temporarily stopped and subsequently restarted. • Dosing permanent discontinuation is defined as when there is no more lorlatinib treatment after stopping lorlatinib treatment.
Time-to-treatment discontinuation (TTD) for lorlatinib	• Defined as time from lorlatinib initiation to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. • Patients who are lost to follow-up will be censored based on the last known contact/visit date.
TTD for the subsequent treatment of lorlatinib	• Defined as time from the initiation of subsequent treatment after lorlatinib to discontinuation of treatment for any reason, including disease progression, treatment toxicity, and death. • Patients who are lost to follow-up will be censored based on the last known contact/visit date.
Real-world ORR of lorlatinib	• Real-world ORR is defined as proportion of patients with a documented tumor response (complete response or partial response as radiologically and/or clinically assessed by primary physician in routine clinical practice) during treatment with lorlatinib. • The definitions of clinical response are as follows; Complete response: Complete resolution of all visible disease. Partial response: Partial reduction in size of visible disease in some or all areas without any areas of increase in visible disease. Stable disease: No change in overall size of visible disease (includes cases where some lesions increased and some lesions decreased in size). Progressive disease: Increase in overall size of visible disease or presence of new lesions.

Outcome	Definition
	Not evaluable: Clinician specifically indicates that response is "indeterminate" or "uncertain" or if clinician's interpretation of the scan(s) cannot be mapped to one of the above categories.
Real-world IC-ORR of lorlatinib for the patients with brain metastasis.	• Real-world IC-ORR is defined as proportion of patients with a documented tumor response (complete response or partial response as radiologically and/or clinically assessed by primary physician in routine clinical practice) for intracranial lesion during treatment with lorlatinib. • The definitions of clinical response for intracranial lesion are as follows; Complete response: Complete resolution of all visible disease for intracranial lesion. Partial response: Partial reduction in size of visible disease for intracranial lesion in some or all areas without any areas of increase in visible disease. Stable disease: No change in overall size of visible disease for intracranial lesion (includes cases where some lesions increased and some lesions decreased in size). Progressive disease: Increase in overall size of visible disease or presence of new intracranial lesions. Not evaluable: Clinician specifically indicates that response is "indeterminate" or "uncertain" or if clinician's interpretation of the scan(s) cannot be mapped to one of the above categories.
Relative dose intensity	• Ratio of treated dose intensity to standard dose intensity using standard drug information
AESIs (CNS AE, Hyperlipidemia, and Edema)	• Collection items were as follows. AE term, onset/end date, ongoing or not, causal relationship to lorlatinib, action taken for lorlatinib, serious event or not, CTCAE Grade at onset, outcome, and concomitant medication. • AE term of CNS AE are classified into five categories: cognitive disorder, speech disorder, mood disorder, hallucination, and unknown.

Abbreviations: NSCLC=non-small cell lung cancer; PFS=progression-free survival; TTD=time-to-treatment discontinuation; CTCAE=Common Terminology Criteria for Adverse Events.

9.4. Data Sources

Study data will be collected from each participating site.
Data will be available in both a structured form and an unstructured form. Unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. Unstructured data will be abstracted manually by a trained research associate into a set of pre-specified data tables by filling up a CRF and subsequently entered into a study-specific EDC via a standardized eCRF interface. The rules of abstraction will be detailed in the (to be developed) abstraction manual.
An assigned and supervised research personnel (e.g., a clinical research coordinator) will later assist the study investigator to transfer the recorded data from the source template to the eCRF. The filled source template will remain as part of the clinical document of the investigator and participating center.
Depending on the CRF design, structure, and complexity, it may also be feasible for the investigator to enter the data directly into the eCRF. Programming of edit checks to identify discrepant data entered and to check for accuracy will be performed.
The eCRF must be signed by the investigator. The signature serves to attest that the information contained on the eCRF is true. At all times, the investigator has the final responsibility for the accuracy and authenticity of all data entered into the eCRFs.

9.5. Study Size

This study is a descriptive study which aims to describe AESIs and effectiveness of lorlatinib in the first line treatment of patients with ALK+ NSCLC, rather than testing any pre-defined hypothesis. Therefore, calculation of sample size and statistical power are not relevant.
The expected number of patients will be approximately 75 patients, with a minimum of 60 patients treated with loratinib in total (the number of patients for “retrospective cases” will be approximately 20).

9.6. Data Management

Investigators will fill out relevant CRFs based on source documents (e.g., patients’ medical charts) by EDC. After the completion of the CRFs, the investigator will promptly submit them.
When receiving a query from the sponsor on the completed CRF (i.e., Data Clarification Form [DCF]), investigators will reconfirm the information on source documents, fill out the DCF as required, and submit the DCF.

9.6.1. Case Report Forms/Data Collection Tools/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 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.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.
If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.
Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.
The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.6.3. Record Disposal

After the storage period has ended, personal information will be handled with utmost care and disposed of in an irretrievable manner, such as by dissolving or shredding paper-based information. Information stored on other media will also be disposed of in a way that it cannot be restored.

9.7. 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.

9.7.1. Analysis Methods

All outcomes will be summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations.
Continuous variables will be summarized using n, means, standard deviations, medians, interquartile ranges (IQRs), minimums and maximums. Categorical variables will be summarized using frequencies (counts) and percentages. For the time-to-event endpoints, e.g. real world PFS/TTD, the Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median real world PFS/TTD with 2-sided 95% confidence intervals (CIs) using Brookmeyer and Crowley method. These endpoints will also be displayed graphically. Censoring rule is shown in Section 9.3.
Depending on sample size, stratified analyses of the time-to-event endpoints (real world PFS/TTD) may be performed based on starting dose of lorlatinib, lorlatinib dose interruption/reduction, presence of central nervous system (CNS) metastasis at baseline as exploratory analyses using Cox proportional hazards model.

9.8. Quality Control

The sponsor will train investigators and study site staff with an onsite training visit or web-training on the protocol, CRFs, and any applicable study processes. Any new information relevant to the performance of this study will be forwarded to the investigator and study site staff during the study. Remote data monitoring will be conducted during the life of the study to ensure timely reporting of data, data integrity, and consistency. CRFs for all included patients will be made available to the remote data monitor for review. The study sites will be queried and managed to request resolution to any issues that may arise during the course of the study.

9.9. Limitations of the Research Methods

1. As this is observational study, there will likely be issues with missing data and data quality. Some information may not be routinely recorded by clinicians or are recorded inconsistently. This will impact the study results and findings.
2. The lack of a comparison group makes it difficult to interpret both safety and effectiveness.
3. Due to limitations in sample size and potential bias in the background of participants, it is not possible to evaluate the relationship between the presence or absence of dose reduction/drug discontinuation and outcomes
4. High-volume centers will be preferentially selected in this study, so enrolled patients may have some specific characteristics. For this reason, the study results may not reflect all Japanese clinical outcomes.
5. There may be qualitative differences between the groups of retrospective cases and prospective cases (changes in conscious/unconscious clinical behaviors, changes in patient awareness regarding side effect reporting, etc.)
6. Given the study period, there is a high possibility that sufficient follow-up may not be possible up to TTD of the next treatment after lorlatinib.
7. Evaluation of disease response may differ at each site, and measurement errors may be included in the estimated value.
8. As we have not excluded those who participated or are participating interventional studies before and after the current treatment, there is a possibility that the frequency of follow-ups may be affected, which could potentially impact the evaluation of outcomes.

9.10. Other Aspects

9.10.1. Report to the chief executive of the study site

Each study site's investigator shall report following to the chief executive of the study site in writing:

1) Facts or information that could undermine the ethical validity or scientific rationality of the study, or information that could potentially do so, and is considered to affect the continuation of the study.
2) Facts or information that could undermine the credibility of the research results, or information that could potentially do so.
3) Protocol and protocol amendments.
4) Progression of the study (every year).
5) Discontinuation and interruption of the study.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. 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 will be stored at the study site in encrypted electronic and 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 investigator 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.

10.2. Provision of Information

The data in this study will be provided to Mebix Inc., a contract research organization, through EDC from the study sites. After conducting data management and statistical analysis, Mebix, Inc. will provide the data set and analysis results to Pfizer.
The record items and recording methods related to the provision and receipt of information in this study are as follows.

Information Provider: Study Sites

Recorded Items	Recording Method
-Name of the information recipient organization -Person in charge of the information recipient organization	Storage of this protocol (the name of the information recipient organization as well as person in charge is described in the separate sheet on the research implementation structure)
-Items of information to be provided	Storage of this protocol (the items of information to be provided are described in '9.3. Variables')
-Names of the study subjects, etc. -The fact that informed consent/appropriate consent has been obtained (in case of receiving informed consent/appropriate consent)	Storage of ICD (in case of obtaining consent in writing), and storage of medical records (in case of obtaining consent verbally/appropriate consent)

Information Recipient: Pfizer Japan Inc. and Medix Inc.

Recorded Items	Recording Method
- Name of the information providing organization	Storage of this protocol (the name of the information providing organization is described in the separate sheet on the research implementation structure)
-Person in charge of the information providing organization	Storage of this protocol (the person in charge of the information providing organization is described in the separate sheet on the research implementation structure)
-Process of collecting the information to be provided	Storage of this protocol (the process of collecting the information to be provided is described in '9.1. Study Design')
-Items of the information to be provided	Storage of this protocol (the items of information to be provided are described in '9.3. Collected Items')
-Location of the information providing organization	Storage of this protocol (the location of the information providing organization is described in the separate sheet on the research implementation structure)
-Name of the head of the information providing organization	Storage of this protocol (the name of the head of the information providing organization is described in the separate sheet on the research implementation structure)

The records of information provision and receipt in this study must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Pfizer have expressly agreed to a different period of retention via a separate written agreement or unless applicable local regulations request.
As for the information provision to foreign countries, the details are not yet determined. Therefore, the name of the foreign country to which the transfer/provision will be made as well as the

information about the measures to protect personal information cannot be specified. The information may be provided to countries where laws and regulations on personal information and privacy are not as sufficient as in Japan. However, the information has been replaced with unique identifiers, so the recipient will not be able to know information that can identify individuals such as the patient's name and address, except for regulatory authorities. In addition, since the destination of the transfer/provision of information may be decided after the end of this study, the possibilities of information provision to foreign countries and conducting review by regulatory authorities to confirm the reliability of the research data through medical records and ICD will be explained to the research subjects or their legally acceptable representatives. The record items and recording methods for the provision and receipt of information will be the same as described above.

10.3. Patient Consent

10.3.1. Informed consent in writing or verbally

The investigator explains participation to patients using the reviewed and approved patient information sheet. An informed consent form is then used to obtain written consent from fully informed patients. The investigator explains that participation in the research is completely voluntary and that subjects are free to withdraw their consent at any time, even after providing consent form. In addition, the attending physician have to take necessary measures to ensure that subjects' rights to self-determination and treatment choice are not limited and that they would not be penalized for refusing or withdrawing consent from participation in the study. The informed consent form will then be revised after institutional review board (IRB)/independent ethics committee (IEC) grants approval, and written consent will be obtained from each subject.
The ICD will be written in a way that is easy for the research subjects to understand, and will include the following explanations:

1) The name of the study and the fact that permission has been obtained from the head of the research institution for this study
2) The names of all the principal investigators and the name of the study sites
3) The objective and significance of the study
4) The method and duration of the study
5) The reason for being selected as a research subject
6) The burden on the research subject and the anticipated risks/benefits
7) The fact that a research subject can withdraw the consent to the study being conducted or continued at any time (if it is difficult to take measures according to the withdrawal from the research subject, include the explanation and the reason for it)
8) The fact that the research subject will not be disadvantaged by not agreeing to the study being conducted or continued, or by withdrawing consent
9) The method of disclosure about this study
10) Upon request from the research subject, within the range that does not hinder the protection of other research subjects' personal information and the originality of this study, the research plan and materials on the research method can be obtained or viewed, and the method of obtaining or viewing them
11) Handling of personal information (including the method of processing)
12) The method of retention and disposal of information

13) The situation regarding conflicts of interest in research funding sources and other research institutions, and personal income and other conflicts of interest in researchers
14) Handling of results regarding this study
15) Response to consultations from research subjects and their related parties (including genetic counseling)
16) Information on the recipient when providing information to a person in a foreign country
17) Economic burden or compensation for research subjects
18) Information about other treatment options if not participating in this study
19) Presence or absence of compensation for health injuries
20) The method to confirm the information about the content (that is assumed at the time of consent, the research to be conducted, and other research institutions that will be provided), if the samples and information obtained from the research subjects may be used for future research that is not specified at the time of consent from the study participants, or may be provided to the other research institutions.
21) The fact that auditors and ethics review committee members will view information about the research subject within the necessary range, assuming that the research subject's confidentiality is protected.

For patients who have transferred to another hospital, written consent is not mandatory, and enrollment by verbal informed consent is allowed. The items to be explained when obtaining informed consent verbally are the same as when obtaining consent in writing, and when informed consent is obtained verbally, the method and content of the explanation and the content of the consent received are recorded in medical records.

If it is difficult to obtain informed consent from the research subject due to lack of consent capacity or other reasons, informed consent is obtained from a legally acceptable representative or equivalent. The explanation and consent obtained from the legally acceptable representative or equivalent is the same as the explanation and consent for the research subject. Also, when explaining and obtaining consent from a legally acceptable representative or equivalent, the description regarding explanation and consent to the research subject in this study protocol is read as 'legally acceptable representative or equivalent' instead of 'research subject' as necessary.
Regarding the legally acceptable representative or equivalent, those who are believed to be able to represent the will and interests of the research subject are selected based on the following conditions:

1. The research subject's spouse, parents, siblings, children, grandchildren, grandparents, cohabiting relatives, or those considered equivalent to these close relatives (excluding minors)
2. The research subject's agent (including a voluntary guardian who has been granted proxy rights)

10.3.2. Appropriate consent in cases where informed consent in writing or verbally is difficult

When there is a risk that obtaining informed consent from the research subject or legally acceptable representative or equivalent, considering the time and cost required to obtain consent, may hinder the implementation of this study, appropriate consent is obtained. When obtaining appropriate consent

from the research subject or legally acceptable representative or equivalent, the content that the investigators should explain is as follows:

1. The purpose and use of the information
2. Even if appropriate consent has been obtained for the implementation or continuation of this study, the research subject or legally acceptable representative or equivalent can withdraw their consent at any time (if it is difficult to take measures according to the withdrawal content, the explanation and the reason for it should be stated).

To obtain appropriate consent, a method of receiving verbal expression of consent is available. When appropriate consent is obtained, the method of explanation and the content of the consent are recorded in the medical record.

10.3.3. Opt-out in cases where informed consent in writing or verbally and appropriate consent are difficult

When there is a risk that obtaining appropriate consent from the research subject or legally acceptable representative or equivalent, considering the time and cost required to obtain consent, may hinder the implementation of this study, enrollment by opt-out is allowed. When investigators enroll by opt-out, they need to disclose the following information to the research subject or legally acceptable representative or equivalent, and provide an opportunity to refuse participation in this study.

1) The purpose and method of using the information (including the fact that it will be provided to other study sites and the method of doing so)
2) The items of information to be used or provided
3) The planned start date for use or provision
4) The name of the study site providing the information and the name of its head
5) The method of obtaining the information to be provided
6) The name of the research representative involved in the research using the provided information and the name of the study site to which the person belongs
7) To stop the use of information that identifies the research subject or the provision to other study sites at the request of the legally acceptable representative of the research subject.
8) The method of accepting the request of the research subject or legally acceptable representative in 7)
9) The information of the recipient, if providing information to a person in a foreign country

10.4. Patient Withdrawal

During the course of this study, the subject can withdraw his/her consent at any time. In any circumstance, every effort should be made to document patient outcomes, if possible. If the patient withdraws from the study and withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. When investigators receive a request from the research subject or legally acceptable representative, to withdraw their consent to participate in this study, they should have them sign and date the consent withdrawal form and confirm the permission to use the data obtained so far. For the data of the research subject who

has requested withdrawal of consent, if permission to use the data is not obtained from the research subject or legally acceptable representative, all such data will be excluded from the analysis. However, if the results of the research have already been published in research articles or conference presentations at the time of withdrawal of consent, it is not possible to exclude the information of the research subject.

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

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs (In the case of a consolidated review, the research representative submits to the representative institutional EC. In the case of an individual review, each principal investigator of the implementing medical site submits to the institutional EC). All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

10.6. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Health, Labor and Welfare (MHLW).

10.7. Anticipated disadvantages and benefits

10.7.1. Disadvantages

This study is conducted within the scope of routine clinical practice, and participating in this study does not entail any special risks or disadvantages. Also, treatment with lorlatinib carries a risk of adverse events, but these can generally occur during treatment in routine clinical practice, and there is no increase in risk attributable to participation in this study.

10.7.2. Benefits

The drug used in this study is approved in Japan. Also, this study is conducted within the scope of routine clinical practice, and all medical expenses, including the cost of the drug during the study period, are paid by the research subject's health insurance and out-of-pocket expenses, so there are no special medical benefits to be gained by the research subject participating in this study. However, while it may not directly benefit the research subject, the results of this research may contribute to the improvement of treatment for NSCLC in the future.

10.7.3. Conflict of interest

This study is conducted with funding from Pfizer. Pfizer provides the funds necessary for the implementation of this study and is involved in the planning and development of the study protocol and the interpretation of the analysis results, but does not directly conduct data collection or statistical analysis. Although the decision-making process regarding the research protocol, analysis,

and publication of this study is discussed between the investigators and Pfizer, there is no deliberate attempt to guide the results in a way that is convenient for Pfizer.
The investigator continuously checks with the investigators, to ensure that no new 'conflicts of interest' that could influence the results and their interpretation have arisen in the planning, implementation, and reporting of this study, and confirms that the implementation of this study does not infringe on the rights of the research subjects.

10.7.4. Response to consultations from research subjects and their associates

The investigators set up a consultation desk for inquiries related to this study from research subjects and their associates, and lists the contact method in the explanatory document (and information disclosure document). The investigators will respond sincerely to all questions received from research subjects and their associates. If they have difficulty responding, they will take measures after consulting with the research representative.

10.7.5. Secondary use of information

The information of the research subject obtained in this study might be used in the future for research that is undetermined at the time the research subject agrees. In that case, it will be implemented after receiving a review from the relevant review committee as a new research and obtaining approval. In addition, at the time of participating in this study, the research subject or legally acceptable representative will be explained about the possibility of future secondary use of the collected information, external provision, and provision to persons in foreign countries.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AEs) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

•All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the data collection tool (e.g., chart abstraction form) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

•Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational

exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

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

•For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for “Illness,” “Study Drug,” and “Drug Name” may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.
All research staff members must complete the following Pfizer training requirements:

• “Your Reporting Responsibilities (YRR) with Supplemental Topics.”

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a “Confirmation of Training Statement” (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training statements must be provided to Pfizer.
Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities (YRR) with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, vendor shall ensure all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

12. Study Registration

Pfizer will register an overview of this research on the European Medicines Agency's website (EMA RWD Catalogues; https://catalogues.ema.europa.eu/search?f%5B0%5D=content_type%3Adarwin_study) and the University Hospital Medical Information Network Center (UMIN-CTR;

https://www.umin.ac.jp/ctr/index-j.htm) prior to implementation, and will update it as appropriate according to changes in the study plan and progress of this study.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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.
The results of this study are not part of any regulatory submission. The results of this study will be submitted for abstracts and publications. The final output will be filed in Pfizer's Global Document Management System upon final study completion.

14. Explanation of results to research subjects

This study is an observational study, and results obtained from routine clinical practice are collected. Therefore, the results obtained in this study will not be explained to the research subject or legally acceptable representative. However, if important results that should be medically informed to the research subject or legally acceptable representative are newly obtained, it will be asked whether they wish to have an explanation. If they do not wish to have an explanation, and the content has a significant impact on life and there is an effective way to deal with it, appropriate action will be taken after hearing the opinion of the ethics review committee.

15. REFERENCES

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16. LIST OF TABLES

17. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable

ANNEX 3. ADDITIONAL INFORMATION

Annex 3A. Description of the Eastern Cooperative Oncology Group (ECOG) Performance Status.

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
5	Dead

Reference: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655.

Annex 3B. Definitions for Tumor, Node and Metastasis (TNM) descriptors.

Grade	T (primary tumor)
T0	No primary tumor
Tis	Carcinoma in situ (squamous or adenocarcinoma)

T1	Tumor ≤3cm
T1mi	Minimally invasive adenocarcinoma
T1a	Superficial spreading tumor in central airways
T1a	Tumor ≤1cm
T1b	Tumor >1 but ≤2cm
T1c	Tumor >2 but ≤3cm
T2	Tumor >3 but ≤5cm or tumor involving: visceral pleura, main bronchus (not carina), atelectasis to hilum
T2a	Tumor >3 but ≤4cm
T2b	Tumor >4 but ≤5cm
T3	Tumor >5 but ≤7cm or invading chest wall, pericardium, phrenic nerve; or separate tumor nodule(s) in the same lobe
T4	Tumor >7cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine; or tumor nodule(s) in a different ipsilateral lobe
	N (regional lymph nodes)
N0	No regional node metastasis
N1	Metastasis in ipsilateral pulmonary or hilar nodes
N2	Metastasis in ipsilateral mediastinal or subcarinal nodes
N3	Metastasis in contralateral mediastinal, hilar, or supraclavicular nodes
	M (distant metastasis)
M0	No distant metastasis
M1a	Malignant pleural or pericardial effusion or pleural or pericardial nodules or separate tumor nodule(s) in a contralateral lobe
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases (1 or >1 organ)

Reference: Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-155.

Annex 3C. Lung cancer stage grouping based on Tumor, Node and Metastasis (TNM) grades.

T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Reference: Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer: Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):138-155.