NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Safety and effectiveness of LORLAtinib as a FIRST-line treatment in an ALK-positive Advanced Non-Small Cell Lung Cancer Spanish population. (LORLA-FIRST).
Protocol number	B7461054
Protocol version identifier	Version 1.0
Date	10 April 2025
EU Post Authorization Study (PAS) register number	EUPAS1000000406
Active substance	Lorlatinib (L01ED05)
Medicinal product	Lorlatinib
Research question and objectives	**Research question** • What is the spectrum of adverse events and mitigation strategies associated with lorlatinib as a first line treatment in an ALK+ NSCLC real-world Spanish population? **Primary Objective** • To describe all the spectrum of the adverse events (AEs) of Lorlatinib (CTCAE v6) and its mitigation strategies, with special interest in CNS AEs **Secondary Objectives** • To identify factors that are predictive of AEs, with special interest in CNS AEs • To evaluate the effectiveness of 1L lorlatinib in real-world practice 1. rwPFS rate at 12 and 18 months in the ITT population with and without brain metastasis at baseline

	2. rwDuration of Response (DoR) 3. rwDuration of Treatment (DoT) 4. rwTime to next therapy/treatment (TTNT) 5. rwSystemic and intracranial Objective Response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1.) criteria 6. rwTime to intracranial progression rate at 12 and 18 months with and without brain metastasis at baseline 7. rwCumulative incidence of brain metastases (BM) in ITT population at 12 and 18 months (with and without baseline BM) 8. rwOverall survival (OS) rate at 12 and 18m
	• To evaluate the impact of lorlatinib on patients' quality of life
	• To describe ALK testing methods used
	Exploratory Objectives (up to 30 patients)
	• To identify neuroimaging markers (Magnetic Resonance Imaging; MRI) that are predictive of the occurrence of CNS AEs
Country(ies) of study	Spain
Author	Luis Fernando García MAS Sr Team Lead [redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic Lymphoma Kinase
BM	Brain metastases
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CTCAE v.6	Common Terminology Criteria for Adverse Events Version 6
ctDNA	Circulating tumour DNA
DOR	Duration of Response
DOT	Duration of the Treatment
DP	Disease Progression
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ C30	European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire C30
FISH	Fluorescent in situ hybridization
HR	Hazard Ratio
ICO	Catalonian Institute of Oncology
IHC	Immunohistochemistry
ITT	Intention-to-treat
IEC	Independent Ethics Committee
MRI	Magnetic Resonance Imaging
NGS	Next Generation Sequencing
NIS	Non-Interventional Study
NSCLC	Non-Small Cell Lung Cancer
NR	Not reached
ORR	Objective Response Rate
OS	Overall Survival
PASS	Post-Authorisation Safety Study
PFS	Progression-Free Survival
PR	Partial Response
PRO-CTCAE	Patient Reported Outcomes version of the common terminology criteria for Adverse events
QoL	Quality of life
RECIST v1.1	Response Evaluation Criteria in Solid Tumors
Rw	Real-World
rwPFS	Real world Progression Free Survival
SAE	Serious Adverse Event
SD	Stable Disease

TKI	Tyrosine-kinase inhibitor
TMB	Tumoral Mutational Burden
TTNT	Time to next therapy/treatment

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
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Dr. Luis Fernando García, MD	MAS Sr Team Lead	Pfizer Oncology	[redacted]

4. ABSTRACT

Title: Safety and effectiveness of LORLAtinib as a FIRST-line treatment in an ALK-positive advanced NSCLC Spanish population (LORLAFIRST)

Version: 1.0, dated 10 April 2025

Principal Investigator(s) of the Protocol

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Rationale and Background

Anaplastic lymphoma kinase (ALK) rearrangements occurred in 3-5% of lung adenocarcinomas[1]. ALK rearrangements stimulate tumor growth and disease progression. During the last decade, multiple ALK inhibitors were developed and demonstrated significant improvement in the clinical outcomes for patients with ALK-positive non-small cell lung cancer (NSCLC). Lorlatinib, a third generation ALK inhibitor, has shown greater potential as a first-line therapy based on the results of the CROWN trial. This was a randomized open-label phase III trial comparing lorlatinib with crizotinib, a first-generation ALK inhibitor, in 296 treatment-naïve patients with advanced ALK-positive NSCLC. With 5yr of follow up, lorlatinib significantly prolonged progression-free survival (PFS) (median PFS not reached 95% CI (64.3 – NR) for lorlatinib arm, and 9.1 months for crizotinib arm (95% CI 7.4 – 10.9), hazard ratio (HR) 0.19 with 95%CI (0.13 – 0.27) by investigator assessment), increased response rates, and enhanced central nervous system (CNS) efficacy compared to crizotinib. In the pivotal phase I/II study, with a median follow-up for OS of 72.7 months (95% CI, 69.3 to 76.3), median OS was NR (95% CI, NR to NR) with lorlatinib, and 5-year OS was 76% (95% CI, 57 to 88) in patients with treatment-naïve ALK-positive NSCLC (n=30)[2] Lorlatinib also had a manageable safety profile consisting of hyperlipidemia, weight gain, and hypertension being the most common G3/4 adverse events[3]. Lorlatinib was associated with adverse events involving the CNS and causing mood/speech and cognitive alterations that generate some uncertainties regarding an adequate management[4]. AT 3yr of follow up of the CROWN study, cognitive functioning scores slightly declined over time in patients with or without CNS AEs, however, this was not clinically significant. Emotional functioning scores generally improved over time, independent of presence or absence of CNS AEs. CNS AEs with lorlatinib were mostly grade 1 or 2 and more than half of all CNS AEs resolved without intervention or with lorlatinib dose interruption[5].

Based on the utilization of lorlatinib in patients who received previous ALK inhibitors, several factors have associated with higher risk of CNS adverse event (AE) such as prior brain

radiotherapy, presence/absence of baseline intracranial metastasis, use of concomitant drugs, or personal clinical history of psychiatric/mood diseases[6]. However, limited data are available about the occurrence of CNS AEs when lorlatinib is used in the first line of treatment (local approval in Spain February 2023) in a real-world population.

On the other hand, lorlatinib has proved its efficacy and safety in clinical trials, but real-world evidence is needed to confirm these results in wider patient populations and to identify prognostic and predictive factors not captured in clinical trials. Ethnicity, molecular variants, and circulating tumour DNA (ctDNA) clearance may influence treatment outcomes and require personalized or combinational approaches.

Research question and objectives

Research question

- What is the spectrum of adverse events and mitigation strategies associated with lorlatinib as a first line treatment in an ALK+ NSCLC real-world Spanish population?

Primary Objective
• To describe all the spectrum of the adverse events (AEs) of Lorlatinib (CTCAE v6.0) and its mitigation strategies, with special interest in CNS AEs
Secondary Objectives
• To identify factors that are predictive of AEs, with special interest in CNS AEs
• To evaluate the effectiveness of 1L lorlatinib in real-world practice 1. rwPFS rate at 12 and 18 months in the ITT population with and without brain metastasis at baseline 2. rwDuration of Response (DoR) 3. rwDuration of Treatment (DoT) 4. rwTime to next therapy/treatment (TTNT) 5. rwSystemic and intracranial Objective Response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. criteria 6. rwTime to intracranial progression rate at 12 and 18 months with and without brain metastasis at baseline 7. rwCumulative incidence of brain metastases (BM) in ITT population at 12 and 18 months (with and without baseline BM)

8. rwOverall survival (OS) rate at 12 and 18m
• To evaluate the impact of lorlatinib on patients' quality of life
• To describe ALK testing methods used
Exploratory Objectives (up to 30 patients)
• To identify neuroimaging markers (Magnetic Resonance Imaging; MRI) that are predictive of the occurrence of CNS AEs

Study Design

The study is an observational, non-interventional, prospective and multicenter trial that evaluates the real-world safety and effectiveness of lorlatinib as a first-line treatment in patients with ALK-positive advanced NSCLC in Spain.

Additionally, our study population exhibits a low incidence of NSCLC patients, approximately 3-4%. Consequently, the current study is descriptive in nature.

Study Population

Patients in 20 Spanish hospitals (clinics, or and primary care centers) must have a confirmed diagnosis of locally advanced and/or metastatic NSCLC with an ALK rearrangement identified by an approved diagnostic test, be older or equal than 18 years and have initiated first-line therapy with lorlatinib at least 7 days and up to 28 days prior to enrolment in the study according to routine clinical practice. They must also sign an informed consent and have a minimum of predetermined data recorded in their medical records. Socio demographic data about the patient's gender, age, height, weight at the treatment initiation will be collected. Additional socio demographic data will be collected: race, along with details regarding their smoking habits, as well as exposure to asbestos and previous personal and family history of cancer, particularly in first-degree relatives. Patients included in clinical trials are also excluded.

Study variables

The following variables will be collected: AE, serious adverse events (SAE), and scenarios involving: exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy; exposure during pregnancy (EDP), occupational/environmental exposure and treatment-associated mortality as well as time to onset and duration of AEs. Likewise, effectiveness variables as rwPFS rate at 12 and 18 months in the ITT population with and without brain; metastasis at baseline, rwDuration of Response (DoR); rwDuration of Treatment (DoT), rwTime to next therapy/treatment (TTNT)M; rwSystemic and intracranial Objective Response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). criteria, rwTime to intracranial progression rate at 12 and 18 months with and without brain metastasis at baseline, rwCumulative incidence of brain metastases (BM) in ITT population at 12 and 18 months (with and without baseline BM), rwOverall survival (OS) rate at 12 and 18m.

Sociodemographic, clinical variables prior to start treatment/on treatment/after treatment with lorlatinib and quality of life data of patients under treatment will be collected.

Data sources

The investigators will collect the data of the patients included in an electronic data collection form (e-CRF) designed specifically for this study and developed by the CRO in charge at the beginning of the study. The data will be stored in an access database protected by password and only accessible to authorized personnel. Descriptive and survival analyses will be performed to evaluate the study objectives, using the Kaplan-Meier method and the Cox model. The AEs will be summarized by presenting the frequency distribution and percentage of these in the total number of patients and will be coded according to the CTCAE v6.0.

Imaging data[9,10]

Brain MRI will be collected at baseline and in case of CNS toxicity. Images will be anonymized and centrally analyzed (See Section 9.3.7) to assess Fazekas scale, morphometric and radiomic features that will be correlated with CNS toxicity.

Baseline CT scan will be collected to determine the body composition. Images will be anonymized and centrally analyzed to assess radiomic features that will be correlated with CNS toxicity. Baseline body CT scan and brain MRI and first tumor assessment will be collected to determine body composition and to compare radiomic characteristics in patients who developed CNS AEs with those who did not.

Study size

In the CROWN trial, the incidence of CNS AEs was 42%[8] and we assumed that the incidence could be higher in the real clinical practice, but it is probably under detected or recorded as most cases are grade 1. We estimated that we need 116 patients treated with lorlatinib in first-line therapy for ALK+ non-small cell lung cancer with an 80% power to detect an incidence of 55% any grade CNS AEs using a 2-sided test.

Data analysis

The safety assessment will be based primarily on the frequency and severity of AE. AEs will be summarized by presenting the number and percentage of these figures in the total number of patients. The absolute and variable frequencies of each AE with respect to the total number of reported AEs will also be presented. Descriptive analyses will be carried out to evaluate the objectives of the study.

Categorical variables will be described by their absolute and relative frequency. Continuous variables will be described with total n, valid n, n unavailable, means, standard deviation, quartiles, minimum and maximum. Survival analysis will be performed using the Kaplan Meier method. A Cox regression model will be carried out to find independent variables associated with overall survival or time until disease progression.

Milestones

- Expected date of approval by the central IEC: 31 May 2025
- Expected date of opening of the first site: 01 June 2025
- Start recruitment: 01 June 2025
- End recruitment: 30 November 2026
- Recruitment period: 18 months
- Expected date for closing of data collection: 30 November 2027
- Interim Analysis after 18m of FUP of first 50 patients included: 30 April 2027
- Expected date of final study report: 31 May 2028

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestones	Planned Date
Registration in the HMA-EMA Catalogues of RWD Studies	03 December 20243rd, 2024 EUPAS1000000406
Expected date of approval by the central IEC	01 May – 31 May 2025
Expected date of opening of the first site	01 June 2025
Start of data collection	01 June 2025
End of recruitment	30 November 2026
End of data collection	30 November 2027
Interim Analysis after 18m FUP of first 50 patients recruited	30 April 2027
Final study report	31 May 2028

7. RATIONALE AND BACKGROUND

Genomic rearrangements involving ALK have been identified in distinct solid tumors including anaplastic large cell lymphoma (ALCL), diffuse large B cell lymphoma, inflammatory myofibroblastic tumor (IMT), glioma, NSCLC, colorectal, breast, ovarian, and esophageal cancer. ALK rearrangements are found in 3-5% of NSCLC, mainly in lung adenocarcinomas[1].

The resulting ALK fusion proteins retain the entire kinase domain of ALK at the C-terminus, and the N-terminus consists of an entirely different protein. These fusion proteins are validated therapeutic targets. Several large international trials have now validated that patients with ALK positive (ALK+) lung cancer benefit from treatment with ALK TKIs, that became the first-line treatment in patients with advanced NSCLC.

Lorlatinib, a third-generation ALK inhibitor, has shown great potential as a powerful and promising treatment option for managing ALK-rearranged NSCLC. Its unique structure and mechanism of action provide several benefits, including strong inhibition of ALK and other related kinases, as well as the ability to cross the blood-brain barrier, targeting a common site of metastasis in NSCLC.

The CROWN trial 5 was a randomized phase III trial that enrolled a total of 296 patients who were randomly assigned to receive either lorlatinib or crizotinib as first-line therapy for ALK-positive NSCLC[7].

At a median of follow up of 60.2 months[4] (95% CI, 57.4 to 61.6) in the lorlatinib group and 55.1 months (95% CI, 36.8 to 62.5) in the crizotinib group. The HR for PFS or death with lorlatinib versus crizotinib was 0.19 (95% CI, 0.13 to 0.27). Median PFS was NR (95% CI, 64.3 to NR) with lorlatinib and 9.1 months (95% CI, 7.4 to 10.9) with crizotinib. The 4- and 5-year PFS was 63% and 60% (95% CI, 51 to 68) with lorlatinib, respectively, and 10% and 8% (95% CI, 3 to 14) with crizotinib. Among patients with baseline brain metastases (measurable and/or non-measurable; n = 35 in the lorlatinib group and n = 38 in the crizotinib group), the HR for PFS or death with lorlatinib versus crizotinib was 0.08 (95% CI, 0.04 to 0.19); median PFS was NR (95% CI, 32.9 to NR) with lorlatinib and 6.0 months (95% CI, 3.7 to 7.6) with crizotinib. Five-year PFS was 53% (95% CI, 35 to 68) with lorlatinib and not evaluable with crizotinib as all patients had progression or death or were censored within 2 years. Among patients without baseline brain metastases, the HR for PFS or death with lorlatinib versus crizotinib was 0.24 (95% CI 0.16 to 0.36); median PFS was NR (95% CI, 64.3 to NR) with lorlatinib and 10.8 months (95% CI, 9.0 to 12.8) with crizotinib. Five-year PFS was 63% (95% CI, 52 to 71) with lorlatinib and 10% (95% CI, 5 to 18) with crizotinib.

Regarding the safety profile of the drug, the median treatment duration was 57.0 months (IQR, 13.9-63.3) with lorlatinib and 9.6 months (IQR, 4.7-17.1) with crizotinib. Overall, 49 of 149 patients (33%) treated with lorlatinib and 36 of 142 (25%) treated with crizotinib had at least one dose reduction. The median relative dose intensity was 99% (IQR, 80-100) with lorlatinib and 99% (IQR, 91-100) with crizotinib. All-causality any-grade AEs occurred in all patients in the lorlatinib group and in 140 of 142 patients (99%) in the crizotinib group; grade 3/4 AEs occurred in 77% and 57% of patients, respectively. A higher rate of grade 3/4 AEs from any cause in the lorlatinib group compared to the crizotinib group was mostly due to hypertriglyceridemia (25% v 0%), hypercholesterolemia (21% v 0%), weight gain (23% v 2%), and hypertension (12% v 1) with lorlatinib, 23% of patients had dose reduction, 62% had temporary treatment interruption, and 11% had permanent discontinuation because of AEs from any cause. Treatment-related AEs caused

permanent treatment interruption in eight patients (5%), which happened in the first 26 months. With crizotinib, 15% of patients had dose reduction, 48% had temporary treatment interruption, and 11% had permanent discontinuation because of AEs from any cause.

Solomon et al reported lorlatinib is associated with neurologic toxicity (mood/speech and cognitive areas), accounting for 35% of patients in the CROWN trial (3yr follow up of the pivotal trial[8]), being in most patients grade 1. CNS AEs did not have a negative impact on patient-reported quality of life. Most CNS AEs resolved (33% without intervention and 17% with lorlatinib dose modification), while 38% were unresolved; most required no intervention. Lorlatinib dose modification did not influence PFS. Few observational studies have reported the frequency of CNS toxicity on patients with ALK+ NSCLC receiving lorlatinib, however no information is available regarding patients from South Europe. The study will be relevant to learn more about the frequency in our population and about the clinical management in real clinical practice.

Lorlatinib also had a manageable safety profile, with hyperlipidemia, weight gain, and hypertension being the most common G3/4 adverse events and some others with lower frequency as the alterations at the CNS level (mood/speech and cognitive) that generate some uncertainties regarding an adequate management. Occurrence of adverse events with lorlatinib in Spain (2nd and later lines approval in February 2021) is known in later lines of treatment and it seems that several factors involved in that previously treated population (use of radiotherapy, presence/absence of baseline intracranial metastasis, use of concomitant drugs, personal clinical history of psychiatric/mood diseases, etc.) are associated to certain types of AEs, i.e. the CNS adverse events[6], but the occurrence of those AEs are not well-known with the use of the drug in the first line of treatment (local approval February 2023) and that is one of the reasons why this data gap with lorlatinib should be covered.

On the other hand, real-world evidence is needed to confirm these results in wider patient populations that are seen in regular clinical practice. For example, ethnicity may be an important factor for how well lorlatinib works. With nearly 50% of the patients in the CROWN trial being Asian, PFS HR was 0.47 (95% CI 0.27-0.82) compared to 0.19 (95% CI 0.11-0.32) in non-Asian origin. In CROWN trial, a highly selected group of patients with ALK-positive NSCLC, 20% of patients had disease progression in the first 12 months of treatment. Also, there was no difference in the rate of progression in the first 4 months of treatment with lorlatinib compared to crizotinib, affecting about 12% of the patients. This high risk of disease progression in the first few months of treatment highlights the need for personalized or combinational approach to prevent early disease progression. Real-world data can offer information on the effectiveness, tolerability, and long-term outcomes of lorlatinib as a first-line therapy, adding to the evidence from controlled clinical trials and may help to identify prognostic and predictive factors not fully captured in clinical trials.

In the CROWN trial, molecular profiling tests were analyzed on plasma cfDNA and tumor tissue samples to examine different genomic changes and their relation to treatment outcomes in patients with ALK-positive NSCLC treated with lorlatinib or crizotinib.

Baseline plasma samples were available from 134 patients in the lorlatinib group and 129 in the crizotinib group2. EML4:ALK variant 1 was found in 15% of patients in the lorlatinib group and 20% in the crizotinib group; EML4:ALK variant 3a/b was found in 13% and 18% of patients, respectively. The median PFS was 64.3 months (95% CI, 26.0 to NR) in patients

with EML4:ALK variant 1 and 60.0 months (95% CI, 33.3 to NR) in those with EML4:ALK variant 3a/b in the lorlatinib group; in the crizotinib group, the median PFS was 7.4 months (95% CI, 5.5 to 9.0) and 5.6 months (95% CI, 5.3 to 7.6), respectively. With lorlatinib (n = 97), the median PFS was 51.6 months (95% CI, 16.4 to NR) in the TP53 mutation–positive subgroup and NR (95% CI, 60.0 to NR) in the TP53 mutation–negative subgroup; with crizotinib (n = 100), the median PFS was 5.7 months (5.4 to 7.2) and 9.1 months (7.6 to 11.1), respectively.

Liquid biopsy results can also give information on ctDNA tumor fraction which are the levels of ctDNA released into the blood (a sign of tumor burden or more aggressive biology). Molecular classification of ALK-positive NSCLC may help make treatment decisions, such as combination strategies, when poor prognosis markers are included at diagnosis.

This protocol outlines the methods for a real-world study that assesses how lorlatinib is used as a first-line treatment in patients with ALK-rearranged NSCLC, focusing on its safety and management. By collecting and analyzing data from different sites in Spain, this study aims to show the real-world clinical outcomes, treatment patterns, and safety of lorlatinib, which will help clinicians make better decisions and improve patient care for ALK-positive NSCLC.

This noninterventional study is designated as a PASS and is conducted voluntarily by Pfizer.

The medical literature contains analogous examples of post-authorization safety studies that offer valuable information[20-22] required by physicians and, in our case, considering that lorlatinib has become the first TKI and biomarker targeted therapy providing the longest efficacy (mPFS not reach after 60.2 months of follow-up in its pivotal trial) reported for all the solid tumors to date[4].

8. RESEARCH QUESTION AND OBJECTIVES

Research question

- What is the spectrum of adverse events and mitigation strategies associated with lorlatinib as a first line treatment in an ALK+ NSCLC real-world Spanish population?

Primary Objective
• To describe all the spectrum of the adverse events (AEs) of Lorlatinib (CTCAE v6.0) and its mitigation strategies, with special interest in CNS AEs
Secondary Objectives
• To identify factors that are predictive of AEs, with special interest in CNS AEs
• To evaluate the effectiveness of 1L lorlatinib in real-world practice 1. rwPFS rate at 12 and 18 months in the ITT population with and without brain metastasis at baseline. 2. rwDuration of Response (DoR)

3. rwDuration of Treatment (DoT) 4. rwTime to next therapy/treatment (TTNT) 5. rwSystemic and intracranial Objective Response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1.) criteria 6. rwTime to intracranial progression rate at 12 and 18 months with and without brain metastasis at baseline 7. rwCumulative incidence of brain metastases (BM) in ITT population at 12 and 18 months (with and without baseline BM) 8. rwOverall survival (OS) rate at 12 and 18m
• To evaluate the impact of lorlatinib on patients' quality of life
• To describe ALK testing methods used
Exploratory Objectives (up to 30 patients)
• To identify neuroimaging markers (MRI) that are predictive of the occurrence of CNS AEs

9. RESEARCH METHODS

9.1. Study Design

This is an observational, non-interventional, prospective, multicenter and nationwide study with the category of PASS (Post Authorization Safety Study), which seeks to answer the research question: what is the spectrum of adverse events and mitigation strategies associated with lorlatinib in a real-world Spanish population? For this purpose, an observational, non-interventional and prospective study design is ideal to faithfully reflect what occurs in the routine clinical practice.

It is important to note that our study population exhibits a low incidence of NSCLC patients, approximately 3-4%. Consequently, the current study is descriptive in nature, as it lacks the statistical robustness (relatively small sample, but almost similar to the total of patients included in the pivotal trial) necessary to establish a significant association between a specific adverse event and the drug.

The primary objective will be to describe all the spectrum of the AEs of lorlatinib (CTCAE v6.0) and its mitigation strategies with special interest in CNS AEs.

Primary Objective	Corresponding Endpoint
• To describe all the spectrum of the adverse events (AEs) of Lorlatinib (CTCAE v6.0) and its mitigation strategies, with special interest in CNS AEs	• Occurrence (number of adverse events) and severity of AEs, with severity determined according to NCI CTCAE v6.0 criteria. Frequency and period of dose reductions as well as concurrent medications used to control AEs will be collected
Secondary Objectives	**Corresponding Endpoints**
• To identify factors that are predictive of AEs, with special interest in CNS AEs	• To evaluate the relationship of multiple demographic and clinical factors with the incidence of AEs, with special interest in CNS adverse events
• To evaluate the effectiveness of 1L lorlatinib in real-world practice	• Effectiveness will be assessed:
1. rwPFS rate at 12 and 18 months in the ITT population with and without brain metastasis at baseline	1. To determine real-world progression-free survival (rwPFS) defined as the time from enrollment to the first occurrence of disease progression (intracranial or systemic) or death from any cause, whichever occurs first, as determined by the investigator using RECIST v1.1. criteria, at 12 and 18 months, in the ITT population with and without brain metastasis at baseline
2. rwDuration of Response (DoR)	2. To determine real world duration of response (DOR), as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1. criteria (or Time from first documentation of CR or PR (whichever occurs first) after index until death or PD)
3. rwDuration of Treatment (DoT)	3. To determine duration of treatment (DoT) as the time from lorlatinib´ s first dose to last dose for any cause. (Time to treatment discontinuation or Time from first dose to last dose of a treatment)

4. rwTime to next therapy/treatment (TTNT)	4. To determine Time to next therapy/treatment (TTNT) as the Time from end of lorlatinib treatment to institution of next therapy
5. rwSystemic and intracranial Objective Response rate (ORR) using RECIST v1.1. criteria.	5. To determine the systemic and real-world intracranial objective response rate (ORR) as determined by the investigator using RECIST v1.1. criteria
6. rwTime to intracranial progression rate at 12 and 18 months with and without brain metastasis at baseline	6. Real world Time to intracranial progression rate at 12 and 18 months with and without brain metastasis at baseline
7. rwCumulative incidence of brain metastases (BM) in ITT population at 12 and 18 months (with and without baseline BM)	7. Real world Cumulative incidence of brain metastases (BM) in ITT population at 12 and 18 months (with and without baseline BM)
8. rwOverall survival (OS) rate at 12 and 18m	8. To determine the real-world overall survival (OS) rate at 12 and 18 months. OS is defined as the time from enrollment to death from any cause
• To evaluate the impact of lorlatinib on patients' quality of life.	• Change from baseline in health-related quality of life (HRQoL), using the EORTC C30, PRO_CTCAE (for CNS AEs) and submodules LC13 at baseline, C1D15, C2D1, C3D1, C6D1 and every 3 months until the 1st year and then every 6 months
• To describe ALK testing methods used	• Describe the different methods used to testing ALK mutations
Exploratory Objectives (up to 30 patients)	**Corresponding Endpoints**
• To identify neuroimaging markers (MRI) that are predictive of the occurrence of CNS AEs	• Fazekas scale, morphometric and radiomic analysis of baseline magnetic resonance images (MRIs) to identify imaging markers associated with the development of CNS AEs

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the countries where this noninterventional study is being conducted.

Sites: The study will be conducted in approximately 20 Spanish hospitals and the participating physicians will be oncologist specialized in the management of NSCLC. [redacted]

Study Visits: All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty in the local Regions where this non-interventional study is being conducted.

This study will use secondary data from electronic medical records (EMR) and primary data (i.e., newly collected data) collected during routine medical assistance in participating Spanish hospitals. Answers of patients to the questionnaires and items will be collected [redacted] Informed Consent must be obtained before patients are included in the study and will be collected in paper format.

All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and healthcare provider specialty where this noninterventional study is being conducted.

Sample size: In the CROWN trial, the incidence of CNS AEs was 42%[8] and we assumed that the incidence could be higher in the real clinical practice, but it is probably under detected or recorded as most cases are grade 1. We estimated that we need **116 patients** treated with lorlatinib in first-line therapy for ALK+ non-small cell lung cancer with an 80% power to detect an incidence of 55% any grade CNS AEs using a 2-sided test.

9.2. Setting

The study population includes adult patients aged 18 years or older diagnosed with non-small cell lung cancer who are carriers of the ALK gene rearrangement recruited in an 18-month estimated period from 20 high specialized hospitals at the country level who have started first-line therapy with lorlatinib according to label prescription, with treatment duration of at least 7 days and up to 28 days.

In Spain, molecular diagnosis of ALK rearrangement is routinely performed in patients with non-small cell lung cancer according to the diagnostic guidelines of the Spanish Society of Pathological Anatomy and the Spanish Society of Medical Oncology. Only patients with a confirmed and valid ALK testing will be included in our cohort. Among validated testing methods are the following: FISH fluorescence in situ hybridisation (FISH) Immnunohistochemistry using the D5F3 clon Roche VENTANA (IHC) mainly, PCR polymerase chain reaction (PCR) ane the next generation sequencing (NGS)[23].

Given the estimated low incidence rate of 3.4% for this disease among the local population[15], and the difficulty of performing molecular testing in some hospitals at the country level, the

Principal Investigators decided to involve centers specializing in the molecular diagnosis of ALK because otherwise, the lack of expertise in the molecular diagnostics would negatively impact the number of patients that can be enrolled in the study.

Based on data from the CROWN trial, where the incidence of CNS AEs was reported to be 42%[8], and assuming that the incidence could be higher in real clinical practice but potentially under-detected or recorded as grade 1 cases, they estimated that 116 patients treated with lorlatinib in first-line therapy for ALK+ non-small cell lung cancer are needed. This would provide 80% power to detect an incidence of 55% any grade CNS AEs using a 2-sided test.

Data collection Periods

Patient data will be collected in the following periods:

- **Pre-index period**: since diagnosis to start lorlatinib treatment.
- **Index Date**: date of start of lorlatinib.
- **Post-index period**: visits performed under clinical practice since index date and until end of study period

Patient data collection will cease at the end of study completion.

Study Visits

The study will be conducted in 5 visits, according to clinical practice:

1. **Baseline visit:** the day on which the patient fulfils the inclusion and exclusion criterion, including signature of the Informed Consent (i.e. the day on which the prospective observation starts) (within cycle 1 if lorlatinib)
2. **Follow-up visit 1**: will be scheduled at month 3 (third cycle of lorlatinib)
3. **Follow-up visit 2**: will be scheduled at month 6 (sixth cycle of lorlatinib)
4. **Follow-up visit 3**: Follow-up visit at month 12 (twelfth cycle of lorlatinib)
5. **Final Visit**: end of follow-up (end of data collection expected November 2027)

Data collection overview

Study Visits and Assessments	Baseline	FU1 C3D1	FU2 C6D1	FU3 C12D1	Final Visit
Informed consent	X				
SOCIO DEMOGRAPHIC DATA					
Medical history	X				
Physical examination including Height and weight	X	X	X	X	X

Study Visits and Assessments	Baseline	FU1 C3D1	FU2 C6D1	FU3 C12D1	Final Visit
Previous personal and family history of cancer	X				
CLINICAL DATA					
ECOG	X	X	X	X	X
Laboratory: Hematology and Blood chemistry (dyslipemia profile included). According to routine clinical practice	X	X	X	X	X
Comorbidities since Index Date: Charlson Index	X	X	X	X	X
Concomitant treatment(s) including previous history of Thromboembolic Disease	X	X	X	X	X
Information of baseline tumor diagnosis: date, staging, (TNM),biopsy, PD-L1 expression, other mutations, etc	X				
Information regarding advanced disease: date, staging, metastatic location, CNS metastasis, previous systemic chemotherapy, radiotherapy, etc	X				
Previous systemic chemotherapy (Yes/No)	X				
Assessments CT scan	X				
Assessments brain MRI	X				
LORLATINIB TREATMENT					
Start, Stop and Discontinuation date	X	X	X	X	X
Dose by cycle	X	X	X	X	X
Reason for discontinuation or for dose reduction	X	X	X	X	X
Evaluation of Treatment Response: method (CT scan, MRI, others) and response	X	X	X	X	X
AFTER LORLATINIB TREATMENT					

Study Visits and Assessments	Baseline	FU1 C3D1	FU2 C6D1	FU3 C12D1	Final Visit
Post-progression treatment: type and palliative care					X
Date of death or last follow-up or last contact					X
QUALITY OF LIVE					
EORTC QLQ C30, LC13	X	X	X	X	X
SAFETY					
PRO-CTCAE	X	X	X	X	X
Adverse Events	X	X	X	X	X

9.2.1. Inclusion Criteria

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

1. Evidence of histologically or cytologically confirmed diagnosis of locally advanced and/or metastatic NSCLC (Stage IV, AJCC v8.0) harboring an ALK rearrangement identified by an approved diagnostic test. (FISH, IHC, RT PCR, Next generation sequencing, NGS)
2. Patients aged ≥18 who have initiated first-line therapy with lorlatinib at least 7 days and up to 28 days prior to enrolment in the study according to routine clinical practice.
3. ALK+ patients with intracranial and extracranial disease are allowed.
4. Patients should have a minimum of 3 months predetermined data recorded in their medical records.
5. Informed consent form personally signed and dated stating that the patient (or their legal representative) has been informed of all relevant aspects of the study.
6. ECOG performance status 0-2.
7. No previous treatment with an ALK TKI (alectinib, brigatinib, ceritinib, crizotinib. Other systemic treatments if previous relapse in early stages are allowed.

9.2.2. Exclusion Criteria

Patients meeting the following criterion will not be included in the study:

1. Patients included in clinical trials are not eligible for this study.

Patient eligibility should be reviewed, documented and confirmed by an appropriately qualified member of the investigator's study team before patients are enrolled in the study.

9.3. Variables

Variable	Role	Data source(s)	Operational definition
Safety			
(1) Serious AEs (SAEs); (2) non-serious AEs (as applicable); and scenarios involving: (3) exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy; (4) exposure during pregnancy (EDP), and (5) occupational/environmental exposure Time to onset and duration of AEs	Outcome measures	Investigators Patient clinical record/Electronic Health record (EHR)	• Adverse Event: An AE is any untoward medical occurrence in a patient administered to a medicinal product. Serious Adverse Event: An 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 SAEs) • Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions) • Results in congenital anomaly/birth defect
Effectiveness			

Variable	Role	Data source(s)	Operational definition
rwPFS rate at 12 and 18 months in the ITT population with and without brain metastasis at baseline.	Outcome measures	Investigators Patient clinical record/Electronic Health record (EHR)	• To determine real-world progression-free survival (rwPFS) defined as the time from enrollment to the first occurrence of disease progression (intracranial or systemic) or death from any cause, whichever occurs first, as determined by the investigator using RECIST v1.1. criteria, at 12 and 18 months, in the ITT population with and without brain metastasis at baseline
rwDuration of Response (DoR)	Outcome measures	Investigators Patient clinical record/Electronic Health record (EHR)	• To determine real world duration of response (DOR), as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined by the investigator according to RECIST v1.1. criteria (or Time from first documentation of CR or PR (whichever occurs first) after index until death or PD)
rwDuration of Treatment (DoT)	Outcome measures	Investigators Patient clinical record/Electronic Health record (EHR)	• To determine duration of treatment (DoT) as the time from lorlatinib´ s first dose to last dose for any cause. (Time to treatment discontinuation or Time

Variable	Role	Data source(s)	Operational definition
			from first dose to last dose of a treatment)
rwTime to next therapy/treatment (TTNT)	Outcome measures	Investigators Patient clinical record/Electronic Health record (EHR)	• To determine Time to next therapy/treatment (TTNT) as the Time from end of lorlatinib treatment to institution of next therapy
rwSystemic and intracranial Objective Response rate (ORR) using RECIST v1.1. criteria.	Outcome measures	Investigators Patient clinical record/Electronic Health record (EHR)	• To determine the systemic and real-world intracranial objective response rate (ORR) as determined by the investigator using RECIST v1.1. criteria.
rwTime to intracranial progression rate at 12 and 18 months with and without brain metastasis at baseline	Outcome measures	Investigators Patient clinical record/Electronic Health record (EHR)	• Real world Time to intracranial progression rate at 12 and 18 months with and without brain metastasis at baseline.
rwCumulative incidence of brain metastases (BM) in ITT population at 12 and 18 months (with and without baseline BM)	Outcome measures	Investigators Patient clinical record/Electronic Health record (EHR)	• Real world Cumulative incidence of brain metastases (BM) in ITT population at 12 and 18 months (with and without baseline BM).
rwOverall survival (OS) rate at 12 and 18m.	Outcome measures	Investigators Patient clinical record/Electronic Health record (EHR)	To determine the real-world overall survival (OS) rate at 12 and 18 months. OS is defined as the time from enrollment to death from any cause.
Socio-demographic data			
Gender	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic	• Male/female

Variable	Role	Data source(s)	Operational definition
		Health record (EHR)	
Age at the treatment initiation	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Time in years between birth date and date of lorlatinib start
Race	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Race (Caucasian, Asian, African, others, unknown or not reported)
Smoking habit	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Never, current, former, unknown). Packs-year
Exposure to asbestos	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Yes, no, unknown).
Previous personal and family history of cancer (first degree relatives).	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Yes, no, unknown).
Socio-economical	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Low/medium/high

Variable	Role	Data source(s)	Operational definition
Height at treatment initiation	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Meters
Weight at treatment initiation (and usual weight prior to diagnosis)	Baseline patient´s characteristic	Investigators Patient clinical record/Electronic Health record (EHR)	• Kg
Clinical data prior to the start of treatment with lorlatinib			
Patient's clinical situation Performance status before the start of treatment lorlatinib by Eastern Cooperative Oncology Group (ECOG)	Baseline characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Baseline autonomy status of the patient by Eastern Cooperative Oncology Group (ECOG)
Baseline Relevant comorbidities (Yes / No) Charlson Comorbidity Index	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Lack of co-morbidity: 0-1 • Low comorbidity: 2 • High Comorbidity: >=3
Past personal or family history of psychiatric or neurological conditions	Baseline patient´s characteristic	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No
Relevant concurrent medications:	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Neurotropic, Psychiatric and mood medication • Anticonvulsants • Other

Variable	Role	Data source(s)	Operational definition
Previous history of Thromboembolic Disease	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No
Events of thrombotic or embolic origin, regardless of location suffered by the patient before the start of lorlatinib and up to 90 days prior to the diagnosis of lung cancer. Type:	Baseline patient´s characteristic	Investigators Patient clinical record/Electronic Health record (EHR)	• Thrombotic/embolic
Events of thrombotic or embolic origin, regardless of location suffered by the patient before the start of lorlatinib and up to 90 days prior to the diagnosis of lung cancer. Location	Baseline patient´s characteristic	Investigators Patient clinical record/Electronic Health record (EHR)	• Superficial / deep
Events of thrombotic or emlic origin, regardless of location suffered by the patient before the start of lorlatinib and up to 90 days prior to the diagnosis of lung cancer. Anticoagulant treatment:	Baseline patient´s characteristic	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No

Variable	Role	Data source(s)	Operational definition
Information of baseline tumor diagnosis Date of first diagnosis. It is considered the first diagnosis as the first record in the confirmatory clinical history of the presence of tumor lesion by biopsy.	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Date format
Tumor staging at diagnosis	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• International TNM Staging system
Tumor staging at the study initiation	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• International TNM Staging System
Histological classification	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• According to World Health Organization Guidelines (WHO Lung cancer 2023).
ALK rearrangement Tested:	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No
ALK Method	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic	• (IHC/FISH/NGS/RNASeq /NanoString/Others: Specify

Variable	Role	Data source(s)	Operational definition
		Health record (EHR)	
ALK Result	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Positive/Negative/ Unknown) per each test
If NGS was performed:	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• ALK fusion partner and EML4 variant, co-occurrence of TP53 mutations
PD-L1 expression	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Tested: Yes/No • IHC Test: • Result (% TPS)
Additional mutational findings:	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• ALK fusion variant • ctDNA tumor fraction • TP53 mutational status • KRAS/BRAF/MAPK/ PI3K/mTOR, RTK, or cell cycle pathway aberrations. • TMB
Information regarding advanced disease Date of first diagnosis (de novo or relapse in early stages).	Baseline characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• The first diagnosis is considered as the first record in the confirmatory clinical history of the presence of the disease
Diagnosis of stage IV disease (Yes/No)	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic	• The first diagnosis is considered as the first record in the confirmatory clinical history of the

Variable	Role	Data source(s)	Operational definition
		Health record (EHR)	presence of metastatic tumor lesion
Type of metastatic locations (check all that apply)	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Locations
Brain metastasis at diagnosis	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Yes/No/Unknown)
Imaging method for brain metastasis screening	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (CT/MRI/None/Unknown)
Brain metastases present at time of lorlatinib initiation	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No
Previous treatments for brain metastasis	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Concomitant steroid treatment (Yes/No) • Symptomatic (Yes/No) • List

Variable	Role	Data source(s)	Operational definition
Surgery	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No. Date
Whole brain radiation Yes/No (Date of last dose)	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Date of last dose)
SRS/radiosurgery	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No (Date of last dose
Has the patient participated in a clinical trial previously?	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Yes/No/Unknown)
Previous radiotherapy	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Yes/No)
Intention of previous radiotherapy	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Curative, palliative

Variable	Role	Data source(s)	Operational definition
Location of previous curative radiotherapy	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Chest, bone, brain, others (specify
Previous systemic chemotherapy	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No
Previous systemic chemotherapy Intention	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Curative (adjuvant or neoadjuvant)
Previous systemic chemotherapy Regimen used	Baseline patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• List
Clinical data during treatment with lorlatinib			
Start and end of treatment	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Date from the first lorlatinib treatment taken and last

Variable	Role	Data source(s)	Operational definition
Starting dose	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• mg
Dose Reduction	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Yes / no) • Date • Reason
Any other mitigation strategies?	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Minimum dose reached • Was the dose increased following a dose reduction? Yes/No • Specify
Temporary interruption of treatment	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Yes / No) • Reason for discontinuation of treatment: progression, toxicity, others
Interruption time (in days)	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Days
Date of progression to treatment	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Date of progression to treatment
Treatment after progression	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic	• (Yes / No).

Variable	Role	Data source(s)	Operational definition
		Health record (EHR)	• Date of definitive discontinuation of treatment
Best tumor response	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Complete response / Partial response / Stable disease / Progression)
Height at maximum tumor response	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Meters
Weight at maximum tumor response	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• kg
In case of CNS disease: Response in CNS	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• (Yes / No / Not documented-evaluable)
Brain progression	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No
Tumor progression location (select all that apply)	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Lung • Brain • Liver • Renal • Other (specify)

Variable	Role	Data source(s)	Operational definition
Re-biopsy at tumor progression	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No
Liquid biopsy performed at progression	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No
Performance status at the time of progression	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Autonomy Status (patient) by ECOG categories
Height at tumor progression	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Meters
Weight at tumor progression	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• kg
Post-progression treatment	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No
Post progression treatment Type	On-treatment patient´s characteristics	Investigators Patient clinical record/Electronic	• Chemotherapy, TKI (specify type), Immunotherapy,

Variable	Role	Data source(s)	Operational definition
		Health record (EHR)	Radiotherapy, Palliative Care.
Post progression treatments	On-treatment patient´s characteristics		• Describe subsequent treatment
Clinical data after lorlatinib completion			
Alive: Yes/No	After-treatment data	Investigators Patient clinical record/Electronic Health record (EHR)	• Yes/No
Date of death or last follow-up	After-treatment data	Investigators Patient clinical record/Electronic Health record (EHR)	• Date format

Variable	Role	Data source(s)	Operational definition
Participant's perspective			
EORTC QLQ-C30	Outcome measure	Baseline, C3D1, C6D1, C12D1, Final visit	ePRO (through mobile device) questionnaire containing 30 questions and assesses the quality of life of oncological participants multidimensionally over 10 subscales.
EORTC QLQ-LC13	Outcome measure	Baseline, C3D1, C6D1, C12D1, Final visit	ePRO (through mobile device) questionnaire for lung participants. The QLQ-LC13 incorporates one multi-item scale to assess lung cancer-associated symptoms (i.e.coughing, haemoptysis, dyspnoea and pain) and side- effects from conventional chemo- and radiotherapy.
PRO-CTCAE (only for CNS AEs)	Outcome measure	Baseline, C3D1, C6D1, C12D1, Final visit	ePRO (through mobile device) questionnaire. When referring to CNS (Central Nervous System) adverse events, the PRO-CTCAE helps in assessing symptoms such as headaches, dizziness, and cognitive changes, which are crucial for understanding the impact of cancer treatments on the nervous system.

Variable	Role	Data source(s)	Operational definition
Exploratory variables (30 patients expected)			
To identify neuroimaging markers (MRI) that are predictive of the occurrence of CNS AEs	Exploratory analysis	MRI	Fazekas scale, morphometric and radiomic analysis of baseline magnetic resonance images (MRIs) to identify imaging markers associated with the development of CNS AEs.

Only variables obtained according to routine clinical practice that follow objectives can and should be documented in this study and follow objectives.

To describe the safety profile of lorlatinib in the patients under the study, the following variables will be collected:

- AE, serious adverse events (SAE), and treatment-associated mortality.
- Time to onset and duration of AEs

Adverse events included in the study database will be coded according to CTCAE v6.0.

To study the safety profile, all adverse events that have been identified since the start of treatment with lorlatinib and related to the drug will be collected in the CRF. (More detail in section 11).

Researchers are reminded of their obligation to notify adverse reactions that the Pharmacovigilance Center as they are aware of.

Quality of Life (QoL) Assessments

Scales will be completed by patients at each study visit:

- **EORTC QLQ C30**: is a cancer-specific quality of life questionnaire (QLQ-C30)[9], which consists of five functional scales (physical, role, cognitive, emotional, and social); nine symptom scales (fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties); and a global health status/quality of life (GHS/QoL). Based on 30 questions in total, the scores range from 0 to 100. This questionnaire was approved and psychometrically validated (as well as each of its translations).
- **QLQ LC13**: the EORTC QLQ-LC13 is a supplementary questionnaire specifically designed for lung cancer patients. It is used in conjunction with the EORTC QLQ-C30 to assess the quality of life in these patients. The QLQ-LC13 focuses on lung cancer-specific symptoms and treatment side effects, such as coughing, shortness of breath, pain, and side effects from chemotherapy[10].

- **PRO-CTCAE (for CNS AEs)**[11]: is a tool developed by the National Cancer Institute (NCI) to capture symptomatic adverse events directly from patients receiving cancer treatment. It includes a set of questions that patients can answer to report the severity, frequency, and interference of symptoms they experience. When referring to CNS (Central Nervous System) adverse events, the PRO-CTCAE helps in assessing symptoms such as headaches, dizziness, and cognitive changes, which are crucial for understanding the impact of cancer treatments on the nervous system.

Exploratory variables (30 patients expected)

The study will capture results/data only from procedures that were actually performed as part of a participant's routine medical care, as determined by their treating physician.

Imaging analysis[12,13]

Brain MRI will be collected at baseline and in case of CNS toxicity. Images will be anonymized and shared to assess Fazekas scale, morphometric and radiomic features that will be correlated with CNS toxicity.

The Fazekas scale will be calculated from the baseline MRI images of each patient. We will qualitatively evaluate the presence of White Matter hyperintensities on FLAIR images using a 4-point rating scale. Specifically, the assigned values for this rating scale were: 0 for no lesions, 1 for focal lesions, 2 for beginning confluence of lesions, and 3 for diffuse involvement of the entire regions with or without the involvement of U fibers.

The morphometric analysis will be completed by studying the volumetry of brain structures, including gray matter, white matter, and cerebrospinal fluid, which will also allow us to define the total intracranial volume. The morphometric analysis will be conducted using the SPM12 software (Welcome Department of Imaging Neuroscience Group) running on MATLAB (Mathworks). In patients with brain metastases at baseline, each of the lesions will be identified and delineated using T1-gadolinium and FLAIR (fluid-attenuated inversion recovery) sequences, utilizing the free image analysis software MRIcron (http://www.mccauslandcenter.sc.edu/mricron/mricron). The contrast-enhancing areas identified in the T1-gadolinium sequence will be defined as the tumor masks (ROI - region of interest). Similarly, the areas outlined in the FLAIR sequence will define the tumor edema compartment. In an initial analysis, the number of lesions, volumetric data (mm^3) for each lesion, and the total sum of all lesions per patient will be calculated, as well as the tumor/edema ratio for each lesion and the sum of all lesions. We will perform an exploratory radiomics analysis, leveraging the masks (ROIs) previously defined in the morphometric analysis. After delineating the ROIs in the previous analysis, several variables related to texture and edge descriptors will be extracted. Weighted averages of each radiomics variable will be obtained for patients with more than one metastatic lesion. These averages will be weighted by the volume of the metastasis. All these parameters will be correlated with the CNS toxicity.

Baseline CT scan will be collected to determine the body composition. Images will be anonymized and shared to assess radiomic features that will be correlated with CNS toxicity.

Central Review

All brain MRIs will be centrally reviewed in [redacted]. Anonymized images with an adequate resolution level that allow for a centralized reading directly on the images, will be collected in a specific platform where the centralized reading will be conducted by central reviewer through a controlled access to the platform and complying with all the current legal requirements regarding data protection.

Central reviewer:

Prof Ernest Nadal

Department of Medical Oncology

ICO Hospitalet, Barcelona (Spain)

9.4. Data Sources

The information that allows to evaluate the primary and secondary objectives of this study will be collected by means electronic case report forms (e-CRFs). Only the investigator and his/her staff can access to this system and enter patient data. Other objectives such as Health related Quality of live assess though PROs, will be collected electronically, using a tablet.

The EORTC QLQ-C30 contains 30 items that cover health issues relevant to a wide range of cancer patients, 24 of which are aggregated into multi-item scales measuring functioning, symptoms (fatigue, pain, and nausea/vomiting), and global health and quality of life (QoL). The remaining six single items evaluate additional cancer-associated symptoms and the perceived economic impact of the disease and treatment[16]. The QLQ-LC13 is a supplementary, lung cancer specific questionnaire with 13 items addressing symptoms associated with lung cancer and its standard treatment[17]. Regarding EORTC QLQ-C30, Cocks et al, performed qualitative interview results from 113 patients with cancer from Europe and the US and showed that concepts included in the QLQ-C30 are widely understood across language versions, and that existing items are relevant to patients across cancer types and disease stages. In this study sample, the 13 most frequently, spontaneously elicited concepts were already covered by the QLQ-C30 conceptual framework. As a conclusion of this assessment, the QLQ-C30 demonstrates good evidence of content validity for the assessment of functional health, symptom burden and health-related quality of life in patients with localised-to-advanced cancer[18]. Bergam et al[17], considers that the results from international field testing lend support to the EORTC QLQ-LC13 as a clinically valid and useful tool for assessing disease- and treatment-specific symptoms in lung cancer patients participating in clinical trials, when combined with the EORTC core quality of life questionnaire.

Regarding PRO-CTCAE questionnaire validity, Dueck et al carried out an assessment with a total of 975 adults with cancer undergoing outpatient chemotherapy and/or radiation therapy enrolled in this questionnaire-based study between January 2011 and February 2012. A total of 940 of 975 (96.4%) and 852 of 940 (90.6%) participants completed PRO-CTCAE items at visits 1 and 2, respectively. At least 1 symptom was reported by 938 of 940 (99.8%) participants. All PRO-CTCAE items had at least 1 correlation in the expected direction with a QLQ-C30 scale (111 of 124, $P < .05$ for all). Stronger correlations were seen between PRO-

CTCAE items and conceptually related QLQ-C30 domains. Scores for 94 of 124 PRO-CTCAE items were higher in the ECOG PS 2 to 4 vs 0 to 1 group (58 of 124, P < .05 for all). Overall, 119 of 124 items met at least 1 construct validity criterion. Test-retest reliability was 0.7 or greater for 36 of 49 prespecified items (median [range] intraclass correlation coefficient, 0.76 [0.53-.96]). Correlations between PRO-CTCAE item changes and corresponding QLQ-C30 scale changes were statistically significant for 27 prespecified items (median [range] r = 0.43 [0.10-.56]; all P <= .006)[19].

Our study will only assess the items related to CNS AEs with PRO-CTCAE.

The research center will be identified with a code, each patient included by this researcher will be identified by a unique number, so that in the central database each patient will be identified by a code of research center and patient number, which in no case will include data that allow identification.

The table that relates the personal data of the patients participating in the study and the identification code assigned to it will be kept only in the investigator's study file of the center and will only be accessible to the research team. In case of inspection by the competent health authorities or internal audit of the sponsor, the inspectors and / or auditors may access to the registry to verify the veracity of the data collected in the study, prior authorization of the IEC/IRB of the center.

Personal data will be treated in accordance with all applicable regulations: according to the Regulation (EU) 2016/679 of the European Parliament and the Council of April 27th, 2016 on Data Protection (GDPR). In Spain, it is regulated by the Organic Law 3/2018, 5th of December, on Personal data protection and digital rights guarantee.

9.5. Study Size

In the CROWN trial, the incidence of CNS AEs was 42%[4] and we assumed that the incidence could be higher in the real clinical practice, but it is under detected as most cases are grade 1. We estimated that we need 116 ALK+ NSCLC patients with an 80% power to detect an incidence of 55% any grade CNS AEs using a 2-sided test. We expect that the recruitment will be completed over a period of one and a half years, as described in the study schedule at 20 sites countrywide.

9.6. Data Management

The investigator will collect data from the enrolled patients in an electronic Case Report Form specially designed for this study.

The patient number we provide is a serial number devoid of any identifying value.

The information is stored in an Access database, which in turn is associated with a file, "WorkGroup", detailing the user code and permits of the investigator within the database. People not within this working group cannot access the database.

A Data Management Plan (DMP) will be developed and once approved by the person responsible for the study, the "Queries" will be programmed in the electronic case form so that when the investigator saves the data, it informs him/her of any doubts regarding the data.

All changes made by the investigators during the collection of data will be stored in a table specially designed for this function indicating the user, date, modified field, the old value and the new value.

9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, 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.

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

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

The study variables will be recorded in an electronic case report form (eCRF) specially designed for the study. Answers of patients to the questionnaires and items will be collected through a tablet and the informed consent to participate in the study will be also collected in paper.

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, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, 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 (eg, 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, 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.

9.7. Data Analysis

General Considerations

The analysis plan will be fully described in a written and approved statistical analysis plan (SAP). The SAP will describe all statistical analyses, including definition of study outcomes and scoring of the different scales, and will further provide a detailed description of analyses to be performed and describe methods to deal with missing data and censoring. The final SAP will include the tables shell to be used for the final data analyses. Moreover, an interim analysis(es) to characterize dropouts and collecting only critical data elements (ie, variables aligned with the study objectives) to minimize site/participant burden will be conducted.

Descriptive analyses will be carried out to evaluate the objectives of the study. In order to describe the profile of the patients under study, a descriptive statistical analysis of each and every one of the variables included in the notebook will be carried out for this purpose.

Categorical variables are described by their absolute and relative frequency. Continuous variables are described with total n, valid n, n unavailable, means, standard deviation, quartiles, minimum and maximum. Progression-free survival will be measured from treatment initiation to evidence of tumor progression or death. Overall survival will be measured from treatment initiation to death. Patients will be censored at last control, if are lost during the follow-up.

The safety assessment will be based primarily on the frequency and severity of AE. AE will be summarized by presenting the number and percentage of these figures in the total number of patients. The absolute and variable frequencies of each AE with respect to the total number of reported AEs will also be presented. If applicable, the codification of the Medical Dictionary for Regulatory Activities (MedDRA)) will be useful Medication will be coded using WHO Drug Dictionary.

Survival analysis will be performed using Kaplan Meier method. A Cox regression model will be carried out to find independent variables associated with overall survival or time until disease progression.

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.

9.8. Quality Control

As this is a post-authorisation study, the same procedures will be followed by the investigator as in routine clinical practice.

However, the investigators are responsible for ensuring that the protocol and Good Clinical Practice (GCP) standards are complied with.

Study sites might be subject to face-to-face or remote monitoring by the person appointed by the sponsor and a review by the Independent Ethics Committee (IEC) and/or quality assurance audits conducted by the relevant regulatory authorities and the study sponsor.

9.9. Limitations of the Research Methods

This is a non-interventional study in clinical practice. Study results might not reflect pivotal clinical trial results, in which patients are assigned to active or control group by chance (through randomization) to reduce errors or bias.

Additionally, our study population exhibits a low incidence of NSCLC patients, approximately 3-4%. Consequently, the current study is descriptive in nature, as it lacks the statistical robustness (relatively small sample, but almost similar to the total of patients included in the pivotal trial) necessary to establish a significant association between a specific adverse event and the drug. The medical literature contains analogous examples of post-authorization safety studies that offer valuable information[20-22] required by physicians and, in our case, considering that lorlatinib has become the first TKI and biomarker targeted therapy providing the longest efficacy (mPFS not reach after 60.2 months of follow-up in its pivotal trial) reported for all the solid tumors to date[4].

Data collected in this study will reflect clinical practice in Spain. As a result, they may not be generalizable to studies conducted elsewhere, due to differences in clinical practice and patient characteristics.

The study is limited to a data collection and does not generate any risk or benefit to the patient. However, this study will allow progress in the knowledge of the conditions and factors associated with the use of lorlatinib.

9.10. Other Aspects

9.10.1. Ethics

This study will be conducted in accordance with the ethical principles that have their origin in the World Medical Association (WMA) Declaration of Helsinki and will be consistent with GCP guidelines and pertinent regulatory requirements.

The study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective task(s).

The study will be conducted in compliance with the protocol. The protocol, any amendments and the patient informed consent will receive IEC/IRB approval/favorable opinion prior to initiation, according to pertinent regulations.

The decision of the IEC/IRB concerning the conduct of the study will be made in writing to the Investigators, and a copy of this decision will be provided to the Sponsor before the beginning of the study. The Investigator and/or the Sponsor is/are responsible for keeping the IEC/IRB informed of any significant new information about the study.

All protocol amendments will be agreed upon by the Sponsor and the Investigator.

Administrative changes of the protocol are minor corrections and/or clarifications that have no impact on the way the study is to be conducted.

This study follows the Spanish law, Royal Decree 957/2020 of 3rd November 2020, which states the guidelines on observational studies for medicinal products for human use.

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/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 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. Patient Consent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/ ethics committee (EC) before use, and available for inspection.

The investigator must ensure that each study patient, or his or her legally acceptable representative is fully informed about the nature and objectives of the study, the sharing of data

relating to the study, and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient or his or her legally acceptable representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative, before any study-specific activity is performed unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each patient's signed consent document.

10.3. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Withdrawal criteria: Patients will receive the study treatment while it is considered to be in their best interest. Specifically, individual treatment of a given patient will continue until:

- Documented disease progression.
- Unacceptable toxicity after allowed dose reductions.
- Intercurrent illness of sufficient magnitude to preclude safe continuation of the study treatment.
- Patient's refusal (follow-up has to be continued for those patients who refuse treatment, but do not withdraw consent) and/or non-compliance with study requirements.
- A major protocol deviation that may affect the risk/benefit ratio for the participating patient.

- Requirement of > 2 dose reductions.
- Investigator's decision.

Patients who are withdrawn for any reasons must not be re-treated in the context of this study at any time. However, if the only reason for discontinuation is disease progression, the patient can be treated beyond radiological progression provided the patient is obtaining benefit from the treatment with good tolerance to the treatment, and the patient and sponsor agrees with the decision.

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained by the investigator. Copies of IRB/EC approvals should be forwarded to Pfizer.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, Royal Decree (RD) 957/2020 of 3 November 2020 regulating non-interventional studies on medicinal products for human use (RD 957/2020), including Royal Decree 577/2013 for safety, and Guideline on Good Pharmacovigilance Practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products, General Data Protection Regulation (GDPR), Organic Law 3/2018, of December 5, on the Protection of Personal Data and the Guarantee of Digital Rights, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP)[14].

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Requirements

Table 6 summarizes the requirements for recording safety events on the CRF and for reporting safety events to the Pfizer Drug Safety Unit (DSU) on the Non-Interventional Study Adverse Event Report Form for Protocols with Stipulated Active Collection of Adverse Events herein after referred to as the NIS AEM Report Form.

These requirements are delineated for 5 types of safety events: (1) serious AEs (SAEs); (2) non-serious AEs (as applicable); and scenarios involving: (3) exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy; (4) exposure during pregnancy (EDP), and (5) occupational/environmental exposure. These events are defined in the section "*Definitions of safety events*".

Table 6. Safety Event Reporting Requirements

Safety event	Recorded on the CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE[a]	All	All
Non-serious AE[a]	All	All
Scenarios involving exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy	All (regardless of whether associated with an AE/SAE)	All (regardless of whether associated with an AE/SAE) Note: Any associated AE/SAE is reported together with the exposure scenario.
Scenarios involving EDP	All (regardless of whether associated with an AE/SAE)	All (regardless of whether associated with an AE/SAE)
Scenarios involving occupational/environmental exposure	Not applicable	All (regardless of whether associated with an AE/SAE)

AE = adverse event; AEM = adverse event monitoring; EDP = exposure to a drug during pregnancy; NIS = non-interventional study; SAE = serious adverse event
[a] for safety events requiring adjudication by the study's external adjudication committee, see details in the Endpoint Adjudication Committee section below.

For each safety event, 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 an SAE (refer to section "Serious Adverse Events" below).

Safety events must be reported as per requirements as described in Table 6 **regardless of whether the event is determined by the investigator to be related to lorlatinib**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer DSU must be made immediately, irrespective of the extent of available event information. This timeframe noted in Table 6 also applies to additional new/follow-up information on previously forwarded safety event reports. If the investigator does not become immediately aware of the occurrence of a reportable safety event, the investigator must report the event within the timelines outlined in Table 6 after learning of it and document the time of their first awareness of the events on the NIS AEM Report Form.

For all safety events submitted to Pfizer DSU, the investigator is required to follow-up until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

In addition, the Pfizer DSU may request that the investigator 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 safety event 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.

Reporting period

For each patient, the reporting period begins at the time of the patient's first dose of lorlatinib 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 lorlatinib within the observation period. A report must be submitted to Pfizer DSU (or its designated representative) for any safety events (as per Table 6) occurring during this period.

If a patient was administered lorlatinib on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.

Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation, the reporting period ends on the date of the decision to not enroll the patient.

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

DEFINITIONS OF SAFETY EVENTS

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
- 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 breastfeeding
- 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.
- Test result requires additional diagnostic testing or medical/surgical intervention.
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- 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.

Serious adverse events

An 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 SAEs)
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- Results in congenital anomaly/birth defect

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. The terms "Disease Progression", "Progression of Disease", or "Malignant disease progression" and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be recorded as AEs or as SAEs in CRF.

Important Medical Event

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.

Suspected Transmission of an Infectious Agent

Additionally, any suspected transmission via lorlatinib 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 lorlatinib. 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 (eg, 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 (eg, patient has no place to sleep)
- Administrative admission (eg, for yearly exam)
- Optional admission not associated with a precipitating medical AE (eg, 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 (eg, for work-up of persistent pre treatment lab abnormality)

Causality assessment

The investigator is required to assess and record the causal relationship.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that lorlatinib caused or contributed to the safety event. For all safety events, sufficient information should be obtained by the investigator to determine the causality.

If the investigator's final determination of causality is "unknown" and s/he cannot determine whether lorlatinib caused the event, the safety event must be reported per the process outlined in Table 6.

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

Endpoint Adjudication Committee

Not applicable

Exposure During Pregnancy, Exposure During Breastfeeding, Environmental Exposure and Occupational Exposure

Exposure during pregnancy

Prospective and retrospective exposure during pregnancy (EDP) reports are reportable using the NIS AEM Report Form and the EDP Supplemental Form, irrespective of the presence of an associated safety event.

The procedures for reporting as per Table 6 should be followed.

If the mother or the fetus experience a safety event during administration of such drugs, the safety event must be reported without the event EDP reported.

An EDP occurs if:

- A female participant becomes, or is found to be, pregnant either while receiving or having been exposed to lorlatinib, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to lorlatinib *(maternal exposure)*.
- A male participant who is receiving or has discontinued lorlatinib inseminates a female partner prior to or around the time of conception and/or during the partner pregnancy.
    - In this case, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to their partner. It must be documented that the study participant was given this letter to provide to their partner.

All reports submitted should include the anticipated date of delivery, as applicable, and should be managed as follows:

- 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 (eg, 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 (eg, 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:

- 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 HCP assesses the infant death as related or possibly related to exposure to investigational product.

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

Exposure during breastfeeding

Exposure during breastfeeding (EDB) is reportable using the NIS AEM Report form, irrespective of whether a safety event has occurred. The procedures for reporting as per Table 6 should be followed.

An EDB occurs if:

· A female participant is found to be breastfeeding while receiving or after discontinuing lorlatinib.

Environmental/Occupational Exposure:

Environmental or occupational exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to lorlatinib. Such exposure may or may not lead to the occurrence of a safety event. Persons at risk for environmental or occupational exposures include healthcare providers, or family members, who may be exposed. Any such exposures to lorlatinib are reportable to Pfizer DSU within the timelines outlined in Table 6 and irrespective of the presence of an associated safety event. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on CRF; however, a copy of the completed NIS SAE Report Form must be maintained in the investigator site file.

Below are examples of environmental/occupational exposure:

- A nonparticipant (a family member or an HCP that has been accidentally exposed to lorlatinib by all possible routes of exposure, eg, ingestion, inhalation, or skin contact and then developed an AE/SAE.
- A male nonparticipant (eg, male family member or a male HCP) who has been exposed to lorlatinib by all possible routes of exposure, eg, ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.
- A female nonparticipant (eg, female family member or female HCP) is found to be pregnant or breastfeeding while being exposed or having been exposed to lorlatinib (ie, environmental exposure) by all possible routes of exposure, eg, ingestion, inhalation, or skin contact.

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 (eg, 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 (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer DSU within the timelines outlined in Table 6, irrespective of the presence of an associated safety event:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by a safety event.
- Medication errors that do not involve a patient directly (eg, 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 and misuse associated with the use of lorlatinib are reported to Pfizer DSU by the investigator, irrespective of the presence of an associated safety event as per Table 6.

Lack of Efficacy

Reports of lack of efficacy of lorlatinib are reported to Pfizer DSU by the investigator, irrespective of the presence of an associated safety event or the indication for use of lorlatinib as per Table 6.

11.1. Single Reference Safety Document

The SmPC/data sheet of lorlatinib will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The single reference safety document should be used by the investigator for prescribing purposes and guidance.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results from interim analyses and final analyses, including subgroup analyses or particular research questions to be further specified in the statistical analysis plan, will be submitted to national or international conferences and/or full-paper publications. Final study results will be filed in Pfizer's Global Document Management System upon final study completion. The final report will be placed at the disposal of the competent higher regional authority within one year after its completion.

In the event of any prohibition or restriction imposed (eg, 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.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

13. REFERENCES

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14. LIST OF TABLES

15. LIST OF FIGURES

None

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

17. ANNEX 2. ADDITIONAL INFORMATION

Not applicable

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