NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Effectiveness of **LOR**latinib as a Real-World, first-line treatment in **ALK**-positive Advanced or Metastatic Non-Small Cell Lung Cancer Patients in Italy (LOR-ALK).
Protocol number	B7461061
Protocol version identifier	Version number 1.1
Date	19 May 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000856
Active substance	Lorlatinib (L01ED05)
Medicinal product	Lorlatinib
Product Reference	• EU-Approval-Numbers: EU/1/19/1355/002 • EU/1/19/1355/003
Procedure Number	Not applicable
Marketing Authorization Holder	[redacted]
Joint PASS	No
Research question and objectives	This is an observational, prospective study involving 70-80 patients, to address the data gaps in the real-world setting on effectiveness, safety, and quality of life data for first-line Lorlatinib treatment. **Research Question:** What is the effectiveness and spectrum of adverse events, therapy management strategies, and patient reported quality of life aspects associated with Lorlatinib as a first-line treatment in an anaplastic lymphoma kinase positive locally advanced or metastatic non-small cell lung cancer real-world population in Italy? **Primary objectives:** • To describe the Progression Free Survival (PFS) rate: PFS rate at 18-months. • To describe Time to the Next Treatment (TTNT) defined as the period from the start of the treatment to the start of the next line of treatment. **Secondary objectives:** • To evaluate first-line Lorlatinib effectiveness in real-world practice: • Real-world objective response rate (ORR)

[redacted]

	• Real-world duration of response (DOR) • Real-world disease control rate (DCR) • Real-world intracranial response rate (IC-RR) • Duration of central nervous system (CNS) intracranial response (IC-DOR) • Time to brain irradiation • Real-world intracranial time to progression (IC-TTP) • Real-world duration of treatment (DOT) • Real-world Progression Free Survival 2 (PFS2) (The time from start of Lorlatinib to the second objective disease progression or death from any cause, whichever occurs first) • Proportion of participants with extracranial progression and sites of progression • Real-world cumulative incidence of brain metastases (BM) at 12 and 18 months (in patients' population with and without baseline BM) • Real World Overall Survival (OS) calculated from the date of the Lorlatinib first dose; OS calculated from the date of aNSCLC diagnosis • Subsequent lines of treatment: ORR, PFS and DOT after Lorlatinib failure for progression of disease or Lorlatinib treatment discontinuation for any reason. • Description of subsequent treatment (chemotherapy or TKI) including type of regimen (chemotherapy or TKI). • To describe anaplastic lymphoma kinase positive (ALK+) locally advanced or metastatic non-small cell lung cancer (aNSCLC) patients' characteristics, as well as disease characteristics, comorbidities, and the history of treatment of lung cancer at initiation of Lorlatinib. • To describe the number of dose reductions, permanent or temporary discontinuation in subjects with ALK+ aNSCLC treated in real-world clinical setting in first-line treatment overall: • Doses and duration of treatment with Lorlatinib • Time to every dose modification (including reason for modification) • Time to discontinuation and reasons for discontinuation • Description of subsequent treatment (chemotherapy or TKI) including type of regimen (chemotherapy or TKI)

	• To describe all the spectrum of the adverse events (AEs) of Lorlatinib based on the common terminology criteria for adverse events version 6 (CTCAE v6)(1):
	  • Percentage of participants with treatment-related Adverse Events (TRAEs)
	  • All AEs, related to Lorlatinib [hyperlipidemia (elevated cholesterol and triglycerides), peripheral neuropathy, and CNS effects]
	
	Exploratory objectives:
	• To describe real-world quality of life (QoL)
	  • European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30(2) and LC13(3)
	  • Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)(4)
	• To describe any resistance mechanism with testing (e.g. liquid biopsy) after disease progression as per clinical practice in each center.

Countries of study	Italy
Authors	[redacted]

Marketing Authorization Holder(s)

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[redacted]

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
AEM	Adverse Event Monitoring
AIOM	Italian Association of Medical Oncology
ALK	Anaplastic Lymphoma Kinase
ALK+	Anaplastic Lymphoma Kinase positive
ARP	Analysis and Reporting Plan
AV	Atrio-Ventricular
aNSCLC	Advanced or Metastatic Non-Small Cell Lung Cancer
BICR	Blinded Independent Central Review
BM	Brain Metastases
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	Central Nervous System
CPR	Clinical Patient Record
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinical Scientist
CSA	Clinical Study Agreement
CT	Computer Tomography
CTCAE v6	Common Toxicity Criteria for Adverse Events version 6
DaM	Data Manager
DCR	Disease Control Rate
DCT	Data Collection Tool
DMP	Data Management Plan
DOR	Duration of Response
DOT	Duration of the Treatment
DSU	Drug Safety Unit
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
EDB	Exposure During Breastfeeding
EDC	Electronic Data Capture
EDP	Exposure During Pregnancy
EEIG	European Economic Interest Grouping
EHR	Electronic Health Record

EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ePRO	Electronic Patient Reported Outcomes
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire C30
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire LC13
FAS	Full Analysis Set
SAS	Safety Analysis Set
FISH	Fluorescence in situ hybridization
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GPP	Good Pharmacoepidemiology Practices
HCP	Healthcare Professional
HMA	Heads of Medicines Agencies
HR	Hazard Ratio
IC	Intracranial
IC-DOR	Intracranial Duration Of Response
IC-RR	Intracranial Response Rate
IC-TTP	Intracranial Time to Progression
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IRB	Institutional Review Board
ISPE	International Society of Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IQR	Interquartile Range
MA	Marketing Authorization
MAS	Medical Affairs Scientist
MD	Medical Doctor
MRI	Magnetic Resonance Imaging
NGS	Next Generation Sequencing
NIS	Non-Interventional Study
NSCLC	Non-Small Cell Lung Cancer
NR	Not Reached
PY	Pack Years
ORR	Objective Response Rate
OS	Overall Survival
PAS	Post Authorization Studies
PASS	Post Authorisation Safety Study
PD-L1	Programmed Cell Death Ligand 1

PFS	Progression-Free Survival
PFS2	Progression Free Survival 2
PR	Partial Response
PRO	Patient Reported Outcomes
PT	Preferred Term
PV	Pharmacovigilance
QLQ	Quality of Life Questionnaire
QoL	Quality of life
RCT	Randomized clinical trials
RNA	Ribonucleic acid
RWE	Real World Evidence
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SmPC	Summary of product characteristics
SDV	Source Data Verification
SOC	System Organ Class
SOP	Standard Operation Procedure
TAT	Turn-around Time
TKI	Tyrosine kinase inhibitor
TNM	Tumor Nodes Metastasis
TRAE	Treatment-related Adverse Events
TTNT	Time to Next Treatment
UICC	Union for International Cancer Control
WMA	World Medical Association
WPAI:GH	Work Productivity and Activity Impairment General Health

3. RESPONSIBLE PARTIES

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Country Coordinating Investigators

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4. ABSTRACT

Title: Effectiveness of LORlatinib as a Real-World, first-line treatment in ALK-positive Advanced or Metastatic Non-Small Cell Lung Cancer Patients in Italy (LOR-ALK)

Version: 1.1, dated 19 May 2026

Principal Investigator(s) of the Protocol

[redacted]

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	MED Oncology RWE/Epi Scientist, Director		[redacted]

Rationale and Background
The CROWN trial showed that Lorlatinib significantly improved the progression-free survival compared to Crizotinib, with a notable protective effect against brain metastases and a manageable safety profile. Based on this trial, Lorlatinib is considered as first-line standard therapy for patients with advanced or metastatic ALK+ NSCLC. This is an observational, prospective study involving 70-80 patients, to address the data gaps in the real-world setting on effectiveness, safety, and quality of life data for first-line Lorlatinib treatment.

Research Question
What is the effectiveness and spectrum of adverse events, therapy management strategies, and patient reported quality of life aspects associated with Lorlatinib as a first-line treatment in an anaplastic lymphoma kinase positive locally advanced or metastatic non-small cell lung cancer real-world population in Italy?

Objectives

Primary objectives
• To describe the Progression Free Survival (PFS) rate: PFS rate at 18-months.
• To describe TTNT defined as the period from the start of the treatment to the start of the next line of treatment.

Secondary objectives

- To evaluate first-line Lorlatinib effectiveness in real-world practice:
  - Real-world objective response rate (ORR)
  - Real-world duration of response (DOR)
  - Real-world disease control rate (DCR)
  - Real-world intracranial response rate (IC-RR)
  - Duration of central nervous system (CNS) intracranial response
  - Time to brain irradiation
  - Real-world intracranial time to progression (IC-TTP)
  - Real-world duration of treatment (DOT)
  - Real-world PFS2
  - Proportion of participants with extracranial progression and sites of progression.
  - Real-world cumulative incidence of brain metastases (BM) at 12 and 18 months (in patients' population with and without baseline BM)
  - Real-world overall survival (OS) calculated from the date of the Lorlatinib first dose; OS calculated from the date of aNSCLC diagnosis
  - Subsequent lines of treatment: ORR, PFS and DOT after Lorlatinib failure for progression of disease or Lorlatinib treatment discontinuation for any reason.
  - Description of subsequent treatment (chemotherapy or TKI) including type of regimen (chemotherapy or TKI)

- To describe ALK+ aNSCLC patients' characteristics, as well as disease characteristics, comorbidities, and the history of treatment of lung cancer at initiation of Lorlatinib.

- To describe the number of dose reductions, permanent or temporary discontinuation in subjects with ALK+ aNSCLC treated in real-world clinical setting in first-line treatment overall
  1. Doses and duration of treatment with Lorlatinib
  2. Time to every dose modification (including reason for modification).
  3. Time to discontinuation and reasons for discontinuation
  4. Description of subsequent treatment (chemotherapy or TKI) including type of regimen (chemotherapy or TKI)

- To describe all the spectrum of the AEs of Lorlatinib according to CTCAE v6(1):
  1. Percentage of participants with Treatment Related Adverse Events (TRAEs)
  2. All AEs, related to Lorlatinib [hyperlipidemia (elevated cholesterol and triglycerides), peripheral neuropathy, and CNS effects]

Exploratory objectives

1. To describe real-world quality of life (QoL)
   - European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30(2) and LC13(3)
   - Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH)(4)
2. To describe any resistance mechanism with testing (e.g. liquid biopsy) after disease progression as per clinical practice in each center.

Study design
This is an observational, non-interventional, prospective, multicenter, wide study with the category of a Post Authorization Safety Study (PASS), which primary endpoint will describe the effectiveness of Lorlatinib as real-world progression free survival, assessed by the physician. The study will be conducted in collaboration between various departments and institutions in Italy. The study type is a non-interventional study (NIS) with a focus on clinical practice, efficacy, therapy management, and quality of life.

Population
This study will prospectively enroll in a competitive way 70-80 adult patients with ALK+ aNSCLC in about 25 study centers in Italy.
The study population includes adult patients aged 18 years or older diagnosed with aNSCLC, who are carriers of the ALK gene rearrangement and are enrolled over an estimated 24-month period from about 25 highly specialized hospitals and offices-based oncologists at the country level.

Variables
The variables to be assessed include:

- Key Covariates: patients' characteristics (age, gender, height, weight, smoking status, histological classification, date at diagnosis, presence of BM, Eastern Cooperative Oncology Group Performance Status (ECOG PS), localization and number of metastatic sites, comorbidities, history of adjuvant/neoadjuvant treatment, prior treatment with other ALK).
- Exposures: medical history (neurocognitive, psychiatric, or cardiovascular background, comorbidities and Charlson Comorbidity Index, concurrent medications, ALK testing method, Turn-around Time (TAT), ALK rearrangement).
- Outcomes: (PFS, TTNT, ORR, DOR, DCR, IC-RR, time to brain radiation, duration of intracranial response, DOT, cumulative incidence of BM in patient population at 12 and 18 months, PFS2, IC-TTP, proportion of patients with extracranial progression and sites of progression, any resistance mechanism with testing (e.g. liquid biopsy) after disease progression as per clinical practice in each center., proportion of patients with oligoprogression, OS as well as PFS, ORR, and DOT for subsequent line after Lorlatinib), QoL and PRO (EORTC QLQ-C30, EORTC QLQ-LC13, WPAI:GH) and safety (AEs, SAEs, non-serious AEs). AE, serious adverse events (SAE), and scenarios involving: exposure during breast feeding, medication error, overdose, misuse, lack of efficacy; exposure during pregnancy (EDP), occupational/environmental exposure and treatment-associated mortality as well as time to onset and duration of AEs.

Data sources
Primary and secondary objectives will be evaluated by means of electronic case report forms (CRFs). Other objectives, such as Health-related QoL assessed through Patient Reported Outcomes (PROs), will be collected electronically with App/website from pts own device or tablets provided to the sites.

Study size
The planned sample size of approximately 70-80 patients is based on feasibility considerations and is intended to provide a descriptive estimate of the progression-free survival (PFS) rate at 18 months under real-world clinical conditions in Italy. For more information see section 9.5.

Data analysis
The analysis will be primarily descriptive, and will rely on all available observed data without any imputation for missing values. For continuous variables, the number of non-missing observations, mean, standard deviation,

minimum, 25th percentile, median, 75th percentile and maximum will be presented. For categorical variables, absolute and relative frequencies will be provided.

The Kaplan-Meier method will be used for time-to-event analyses (PFS, TTNT, DOR, duration of intracranial response, time to brain irradiation, DOT, PFS2, OS, DOT and PFS of subsequent lines of treatment), including the primary endpoints of PFS and TTNT. Time-to-event variables will be presented with survival rates at specified time points, lower quartile, median, upper quartile and the respective 95% confidence limits. Frequency of the number of events will be given, and a Kaplan-Meier plot will be provided.

Statistical analyses of collected data will be further documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the sponsor. Analyses will be conducted using standard statistical analysis software products (e.g., the latest version of SAS).

Milestones

Milestone	**Planned Date**
Expected date of approval by the central IEC in Italy	31 May 2026
Start of data collection	01 July 2026
Planned date of end of data collection	01 January 2030
Interim analysis after 18 months	01 January 2028
Date of protocol registration in the HMA-EMA catalogues of real-world studies	24 November 2025
Final study report	01 May 2030

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
Version 1.1	19 May 2026	Administrative	Cover page Header Abstract	The protocol date and version were updated	Updated to avoid discrepancy.

6. MILESTONES

Milestone	Planned Date
Expected date of approval by the central IEC in Italy	31 May 2026
Start of data collection	01 July 2026
Planned date of end of data collection	01 January 2030
Interim analysis after 18 months	01 January 2028
Date of protocol registration in the HMA-EMA catalogues of real-world studies	24 November 2025

Final study report	01 May 2030

7. RATIONALE AND BACKGROUND

Lung Cancer

NSCLC is the most common cause of fatal malignancy globally, most often diagnosed in advanced stages, where surgery and local radiotherapy are no longer curative or indicated.(5) A subgroup of non-squamous NSCLC patients harbors driver mutation in ALK rearrangements. ALK+ NSCLC is diagnosed worldwide in approximately 40,000 to 75,000 people per year. This subtype of lung cancer affects about 5% of patients with aNSCLC.(6)

In Italy, the standard therapy for advanced stages of ALK+ NSCLC primarily involves the use of ALK TKIs. These targeted therapies have shown significant efficacy in improving PFS and ORR as well as QoL improvement and delayed deterioration in patients with ALK+ aNSCLC.(7)

Lorlatinib

Lorlatinib is a third-generation inhibitor targeting ALK. It was designed as a macrocyclic molecule to enhance selectivity and potency, particularly against a wide spectrum of ALK resistance mutations that have emerged in clinical settings. Unlike earlier-generation ALK inhibitors, Lorlatinib demonstrates superior activity in both biochemical and cellular models, and its molecular structure allows it to effectively penetrate the blood–brain barrier, achieving therapeutic concentrations in the CNS.(8)

This CNS permeability is especially critical for patients with ALK+ NSCLC, as BMs are a common complication. In early-phase clinical trials (Phase I and II), Lorlatinib showed robust antitumor efficacy in patients who had previously received first-generation, second-generation ALK inhibitors, or both. Notably, it produced significant intracranial responses, including individuals with leptomeningeal disease, a particularly aggressive form of CNS involvement.(9, 10) Based on the efficacy and safety data from the phase III CROWN trial(11-13), Lorlatinib is considered the standard treatment for ALK+ aNSCLC patients as of today.(7, 14, 15)

Beyond its clinical performance, Lorlatinib's development reflects a strategic shift toward overcoming acquired resistance and addressing the unmet needs of patients with CNS progression. Its broad mutation coverage and CNS activity position it as a key therapeutic option in the evolving landscape of targeted lung cancer treatments.

CROWN trial

The CROWN trial (NCT 03052608) is a global, randomized, phase III trial comparing Lorlatinib with Crizotinib (the standard-of-care first-line treatment at the time of trial initiation) in patients with previously untreated ALK+ aNSCLC. Here, we report the results of the CROWN trial.

At the interim analysis, Lorlatinib showed improved benefit over Crizotinib in patients with previously untreated ALK+ aNSCLC. Median PFS by blinded independent central review (BICR) was not reached (NR) with Lorlatinib (95% confidence interval (CI) NR to NR) and 9.3 months (95% CI 7.6 to 11.1) with Crizotinib with a hazard ratio (HR) of 0.28 (95% CI 0.19 to 0.41; p<.001).(11) Based on these results, Lorlatinib received regulatory approval in 2021 in patients with previously untreated, ALK+ aNSCLC.(16, 17)

In a subsequent post hoc analysis after approximately 3 years of follow-up, Lorlatinib continued to show superior PFS benefit over Crizotinib irrespective of the presence or absence of baseline BM. At a median follow-up of 36.7 months in the Lorlatinib group, median PFS by BICR was still NR (95% CI NR to NR) and time to intracranial progression by BICR was also longer with Lorlatinib than with Crizotinib in the overall patient population. Merely,

one patient developed intracranial lesions on Lorlatinib treatment, suggesting a protective effect of Lorlatinib against the development of BM.(12)

Given that median PFS was not reached after 3 years of follow-up, a post-hoc analysis was performed to evaluate a long-term systemic and intracranial outcome from the CROWN study at the clinically meaningful landmark follow-up of 5 years. Lorlatinib was found to have superior efficacy to the first-generation ALK TKI Crizotinib and the median PFS was NR (95% CI 64.3 to NR) compared to 9.1 months with Crizotinib (HR 0.19; 95% CI 7.4 to 10.9). 60% of patients had not progressed on Lorlatinib. More than half of patients were progression-free after 5 years. For patients with baseline BM, the HR for PFS was 0.08. Among patients with baseline BM, the intracranial activity was significant with an HR for intracranial PFS of 0.08. At the five-year mark, 92% of patients had not experienced intracranial progression. The median DOT varied by group, with 57.0 months (interquartile range (IQR) 13.9 to 63.3) for Lorlatinib, compared with 9.6 months (IQR 4.7 to 17.1) for Crizotinib, respetively.(13)
Overall, 49 of 149 patients (33%) treated with Lorlatinib and 36 of 142 (25%) treated with Crizotinib had at least one dose reduction. Lorlatinib exhibits a unique safety profile compared to other ALK TKIs, characterized by hyperlipidemia and CNS effects. 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. The higher incidence of all-causality grade 3/4 AEs in patients in the Lorlatinib group versus Crizotinib group was largely due to hypertriglyceridemia (25% versus 0%), hypercholesterolemia (21% versus 0%), weight gain (23% versus 2%), and hypertension (12% versus 1%). With Lorlatinib, all-causality AEs led to dose reduction in 23% of patients, temporary treatment discontinuation in 62%, and permanent discontinuation in 11%. TRAEs led to permanent treatment discontinuation in eight patients (5%), which occurred during the initial 26 months. With Crizotinib, all-causality AEs led to dose reduction in 15% of patients, temporary treatment discontinuation in 48%, and permanent discontinuation in 11%.

At 5 years, all-causality any-grade cardiovascular AEs occurred in 42 of 149 patients (28%) in the Lorlatinib group and 40 of 142 (28%) in the Crizotinib group. Among patients with hyperlipidemia that was either present at baseline or developed during the study, 37 of 134 patients (28%) in the Lorlatinib group and 15 of 32 (47%) in the Crizotinib group had cardiovascular AEs. The lower incidence of cardiovascular AEs in this patient population in the Lorlatinib group versus Crizotinib group was largely due to ischemic heart disease (16% versus 31%) as well as embolic and thrombotic events (7% versus 19%). All-causality CNS AEs occurred in 42% of patients in the Lorlatinib group, the majority of which (86%) were of grade 1/2 severity. Only three patients who experienced treatment-related CNS AEs (two had confusional state and one had nightmares) permanently discontinued Lorlatinib. In the Lorlatinib group, CNS AEs occurred in six out of nine (67%) patients who had prior brain radiotherapy and in 57 of 140 (41%) patients without prior brain radiotherapy.(13)

Lorlatinib exhibited a distinct safety profile compared to Crizotinib, characterized by a higher incidence of certain AEs, but an overall manageable toxicity pattern. Patients treated with Lorlatinib more frequently experienced grade 3/4 AEs such as hypertriglyceridemia (25% versus 0%), hypercholesterolemia (21% versus 0%), weight gain (23% versus 2%), and hypertension (12% versus 1%) than those receiving Crizotinib. Overall, grade 3/4 AEs occurred in 77% of patients on Lorlatinib versus 57% on Crizotinib, with TRAEs of grade 3/4 reported in 66% and 39% of patients, respectively. Consequently, temporary treatment interruptions were more common with Lorlatinib (62%) than with Crizotinib (48%). Nonetheless, permanent discontinuation due to TRAEs remained low in both groups (5% with Lorlatinib and 6% with Crizotinib). Dose reductions were required in 33% of Lorlatinib-treated patients and 25% of those on Crizotinib, without significantly affecting the median PFS or IC-TTP.(13)

CNS AEs of any cause were reported in 42% of patients receiving Lorlatinib, however, only three patients discontinued treatment permanently. Most CNS AEs (86%) were mild to moderate (grade 1/2) and occurred more frequently in patients who had undergone prior brain radiotherapy (67%) compared to those who had not (41%). Cardiovascular AEs occurred at similar overall rates in both treatment groups (28%), though their nature differed. Among patients with pre-existing or treatment-emergent hyperlipidemia, cardiovascular events were more frequent

in the Crizotinib group (47%) than in the Lorlatinib group (28%). This difference was primarily driven by fewer ischemic heart events (16% versus 31%) and thromboembolic complications (7% versus 19%) in patients treated with Lorlatinib.(13)

Clinical trial data indicates that most AEs can be effectively managed or reversed through dose modification, such as interruptions or reductions, or with concomitant medications. These adjustments do not compromise the clinical efficacy or QoL for patients.(13)

Real-world evidence is needed to confirm these findings in broader patient populations treated in routine clinical practice as well as refine patient selection and therapeutic strategies in ALK+ aNSCLC. The use of Lorlatinib as first-line treatment in clinical practice has increased over the last year due to unprecedented PFS data, but remains limited by the continued use of Alectinib, former first-line standard-of-care that has demonstrated high efficacy and good tolerability over long-term use. This, along with the low incidence of ALK+ aNSCLC, and the Lorlatinib's safety perception, impacts on the overall Lorlatinib usage. For investigation of the benefits of Lorlatinib in the real-world practice, it is important to understand its post-marketing use and incidence of AEs, therapy management strategies, impact on therapy effectiveness, and patient QoL.

This non-interventional study (NIS) is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

For lung cancer, real-world data will contribute to understanding the therapeutic environment in Italy as well as the local treatment strategies with a focus on practicing pulmonologists/oncologists.

To address data gaps in first-line treatment with Lorlatinib, we initiate a prospective, multicenter, observational, real-world cohort study. This study will enroll in a competitive way 70-80 adult patients with ALK+ aNSCLC who are eligible for first-line treatment with Lorlatinib in clinical practice.

This study aims to provide valuable real-world data to contribute to understanding of Lorlatinib's effectiveness and safety in a broader patient population seen in regular clinical practice. The research question reads as follows:

Research question
What is the effectiveness and spectrum of adverse events, therapy management strategies, and patient reported quality of life aspects associated with Lorlatinib as a first-line treatment in an anaplastic lymphoma kinase positive locally advanced or metastatic non-small cell lung cancer real-world population in Italy?

This study will gather data on patient's profiles receiving first-line Lorlatinib (including age, comorbidities, concurrent medications, therapy management, and dosage) and address the following objectives:

Primary objectives
• To describe the PFS rate: PFS rate at 18-months.
• To describe TTNT defined as the period from the start of the treatment to the start of the next line of treatment.
Secondary objectives
• To evaluate first-line Lorlatinib effectiveness in real-world practice:

• Real-world objective response rate (ORR) • Real-world duration of response (DOR) • Real-world disease control rate (DCR) • Real-world intracranial response rate (IC-RR) • Duration of central nervous system (CNS) intracranial response (IC-DOR) • Time to brain irradiation • Real-world intracranial time to progression (IC-TTP) • Real-world duration of treatment (DOT) • Real-world Progression Free Survival 2 (PFS2) (The time from start of Lorlatinib to the second objective disease progression or death from any cause, whichever occurs first) • Proportion of participants with extracranial progression and sites of progression. • Real-world cumulative incidence of brain metastases (BM) at 12 and 18 months (in patients' population with and without baseline BM) • Real-world overall survival (OS) calculated from the date of the Lorlatinib first dose; OS calculated from the date of aNSCLC diagnosis • Subsequent lines of treatment: ORR, PFS and DOT after Lorlatinib failure for progression of disease or Lorlatinib treatment discontinuation for any reason • Description of subsequent treatment (chemotherapy or TKI) including type of regimen (chemotherapy or TKI).
• To describe ALK+ aNSCLC patients' characteristics, as well as disease characteristics, comorbidities, and the history of treatment of lung cancer at initiation of Lorlatinib.
• To describe the number of dose reductions, permanent or temporary discontinuation in subjects with ALK+ aNSCLC treated in real-world clinical setting in first-line treatment overall: • Doses and duration of treatment with Lorlatinib • Time to every dose modification (including reason for modification) • Time to discontinuation and reasons for discontinuation • Description of subsequent treatment (chemotherapy or TKI) including type of regimen (chemotherapy or TKI).
• To describe all the spectrum of the AEs of Lorlatinib according to CTCAE v6(1): 1. Percentage of participants with treatment-related Adverse Events (TRAEs) 2. All AEs, related to Lorlatinib [hyperlipidemia (elevated cholesterol and triglycerides), peripheral neuropathy, and CNS effects].
Exploratory objectives
• To describe QoL 1. EORTC QLQ-C30(2) and QLQ-LC13(3) 2. WPAI:GH(4)
• To describe any resistance mechanism with testing (e.g. liquid biopsy) after disease progression as per clinical practice in each center.

9. RESEARCH METHODS

9.1 Study Design

This is an observational, non-interventional, prospective cohort, multicenter, and exploratory wide study with the category of a voluntary PASS, which primary endpoint will describe the effectiveness of Lorlatinib as real-world PFS, assessed by the physician.

The study will be conducted in collaboration between various departments and institutions in Italy. The study type is a NIS with a focus on clinical practice, efficacy, therapy management, and QoL aiming to provide valuable real-world data to contribute to understand of Lorlatinib's effectiveness and safety in a broader patient population seen in regular clinical practice.

Approximately 70-80 participants with ALK+ aNSCLC who are eligible for first-line treatment with Lorlatinib in clinical practice, will be enrolled in the study. The Follow-up time will be 18 months for each patient.

The rationale for conducting a prospective cohort non-interventional study (NIS) on Lorlatinib is to generate real-world evidence on its effectiveness, safety, and treatment management in routine clinical practice, as patients treated outside clinical trials often differ from those enrolled in randomized studies.

This will bridge the gap between highly controlled randomized clinical trials (RCTs) and actual clinical practice. By collecting data forward in time (prospectively) from diverse patient populations, these studies improve the limitations of retrospective studies while capturing a more generalizable picture of treatment effectiveness. *(Rivera D et al Oncologist . 2022 Feb 22;27(2):79–81)*

In particular, the NIS aims to assess long-term outcomes, central nervous system effectiveness, adverse event management, and quality of life under real-world conditions, thereby complementing and validating the results of the CROWN trial.

The prospective approach, starting from treatment start, enables systematic and standardized collection of quality of life (QoL) data over time, providing insight into patient-reported outcomes in daily clinical care. Overall, this design allows for a realistic assessment of treatment patterns, patient experience, and therapy management in a real-life setting.

While phase III randomized trials establish the efficacy of targeted oncologic therapies under controlled conditions, their restrictive eligibility criteria and limited follow-up may reduce generalizability to routine clinical practice. Non-interventional real-world cohort studies complement phase III trials by evaluating effectiveness, safety, and treatment use in broader and more representative patient populations, thereby providing essential post-approval evidence for targeted therapies.(20)

Note: "Enrolled" means a participant or their legally authorized representative has provided agreement to participate in a clinical study following completion of the informed consent process.

Table 1 Objectives and Endpoints

Primary objectives	Corresponding endpoints
• To describe the PFS rate: PFS rate at 18-months.	• PFS defined as time from initiation of first-line Lorlatinib to the first occurrence of disease progression or death from any cause assessed by the physician at 18-months.
• To describe TTNT defined as the period from the start of the treatment to the start of the next line of treatment.	• TTNT defined as the period from the start of the treatment to the start of the next line of treatment

	or death from any cause, whichever comes first during the study.
Secondary objectives	**Corresponding endpoints**

• To evaluate first-line Lorlatinib effectiveness in real-world practice:
  • ORR
  • DOR
  • DCR
  • IC-RR
  • Duration of CNS intracranial response
  • Time to brain irradiation
  • IC-TTP
  • DOT
  • PFS2
  • Proportion of participants with extracranial progression and sites of progression
  • Cumulative incidence of BM at 12 and 18 months (in patients' population with and without baseline BM)
  • OS calculated from the date of the Lorlatinib first dose; OS calculated from the date of aNSCLC diagnosis
  • Subsequent lines of treatment: ORR, PFS DOT and OS after Lorlatinib failure for progression of disease or Lorlatinib treatment discontinuation for any reason
  • Description of subsequent treatment (chemotherapy or TKI) including type of regimen (chemotherapy or TKI).
	• ORR defined as the percentage of patients with partial response (PR) or complete response (CR) to Lorlatinib evaluated by physician;
	• DOR measured from the date of first Lorlatinib tumor response to the date of disease progression or death from any cause during the study;
	• DCR defined as the percentage of patients with CR or PR or stable disease (SD) at least for 3 months to Lorlatinib evaluated by physician;
	• IC-RR defined as the proportion of participants with an intracranial CR or PR as response during the Lorlatinib treatment defined according to physician;
	• Duration of CNS intracranial response defined as the time from the first documentation of objective cerebral response to the first documentation of cerebral relapse or death from any cause during the study;
	• Time to brain irradiation defined as time to treatment with stereotactic or whole brain irradiation. For patients with or without BM at baseline;
	• IC-TTP defined as time from treatment initiation until IC disease progression;
	• DOT measured from the date of Lorlatinib first dose to the date of treatment discontinuation or death from any cause during the study;
	• PFS2 calculated in full analysis set (FAS) as the time from initial treatment start to the second documented disease progression or death from any cause during the study;
	• Proportion of participants with extracranial progression and sites of progression, assessed by the treating physician;
	• Cumulative incidence of BM from start of Lorlatinib at 12 and 18 months (in patients' population with and without baseline BM);
	• OS calculated from the date of the Lorlatinib first dose; OS calculated from the date of aNSCLC diagnosis;

	• Subsequent lines of treatment: ORR, PFS, DOT and OS after Lorlatinib failure for progression of disease or Lorlatinib treatment discontinuation for any reason;
• To describe ALK+ aNSCLC patients' characteristics, as well as disease characteristics, comorbidities, and the history of treatment of lung cancer at initiation of Lorlatinib.	• Age, gender • Height, weight • Smoker status: should be differentiated into never smokers and current smokers. In all patients the exact number of PY with start and stop of smoking should be recorded • Histology • Date of diagnosis • Presence of BM at baseline visit (start of Lorlatinib) • ECOG PS at baseline • Localization and number of metastatic sites at diagnosis • History of previous curative lung cancer: adjuvant treatment (surgery, radiotherapy, chemotherapy, Alectinib) • Medical history: neurocognitive, psychiatric, cardiovascular background, and other comorbidities as well as Charlson Comorbidity Index • Comedication • Description of ALK testing methods used in Italy • Turn-around time (TAT) of ALK-testing • Lorlatinib starting dose • Time from diagnosis to initiation of Lorlatinib
• To describe the number of dose reductions, permanent or temporary discontinuation in subjects with ALK+ aNSCLC treated in real-world clinical setting in first-line treatment overall • Doses and duration of treatment with Lorlatinib • Time to every dose modification (including reason for modification) • Time to discontinuation and reasons for discontinuation	• Doses and duration of treatment with Lorlatinib • Date and dose modification (including reason for modification) and timepoint of dose modification. • Date and reason for interruption and/or discontinuation • Description of subsequent treatment (chemotherapy, TKI, immunotherapy, radiation) including type of regimen (chemotherapy or TKI) • ORR, DOR, PFS, and DOT are collected for subsequent treatments after Lorlatinib failure
• To describe all the spectrum of the AEs of Lorlatinib according to CTCAE v6(1):	• Percentage of participants with TRAEs

• Percentage of participants with TRAEs.
• All AEs, related to Lorlatinib [hyperlipidemia (elevated cholesterol and triglycerides), peripheral neuropathy, and CNS effects]
	• discontinuation rates and reasons for discontinuation
	• dose reduction/interruption rates
	• AESIs related to Lorlatinib:
	  • weight gain, cholesterol and triglycerides increase;
	  • peripheral neuropathy;
	  • CNS effects: psychosis, cognitive, mood, and speech AEs.

Exploratory objectives	**Corresponding endpoints**

• To describe QoL
  • EORTC QLQ-C30(2) and QLQ-LC13(3)
  • WPAI:GH(4)
	• Change of baseline visit results and follow-up visits results from the questionnaires

• To describe any resistance mechanism with testing (e.g. liquid biopsy) after disease progression as per clinical practice in each center.	• Method of testing (e.g. NGS (DNA/RNA (ARCHER)), liquid biopsy) • Results: ALK domain resistance mutation, rearrangement loss, and bypass resistance mutation or aNSCLC histological switch

9.2 Setting

This is a prospective, non-interventional, multicenter real-world study (PASS/NIS) evaluating first-line Lorlatinib in 70-80 patients with ALK-positive advanced or metastatic NSCLC in Italy with a 24-month enrollment period from 2026 to 2028 followed by a follow up period until early 2030. The primary objectives are to assess 18-month progression-free survival and time to next treatment, with secondary endpoints covering effectiveness, intracranial outcomes, subsequent therapies, safety, and treatment management. The study also evaluates quality of life and work productivity using validated patient-reported outcome instruments. In addition, it includes a discussion of the representativeness of the enrolled real-world population and any sampling strategies used to ensure adequate coverage across participating centers and countries.
The study population is considered representative of routine clinical practice in Italy, as patients are recruited from both office-based oncologists and academic lung cancer centers. This broad center selection was intentionally chosen to capture different care settings and treatment pathways. Given the rarity of ALK-positive advanced or metastatic NSCLC, a wide and inclusive recruitment approach was applied rather than formal sampling stratification. This pragmatic strategy aims to reflect real-world heterogeneity and enhance the external validity of the study findings.
The study population includes adult patients aged 18 years or older diagnosed with aNSCLC in Italy, who are carriers of the ALK gene rearrangement. Molecular diagnosis of ALK rearrangement is routinely performed in patients with NSCLC according to the diagnostic guidelines of the Italian Association of Medical Oncology (AIOM).(14) Given the estimated low incidence rate of 4-5% for this disease among the local population (22), the Sponsor decided to involve centers specialized in the molecular diagnosis of ALK.

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 the overall study conclusion (42 months from first Subject In) or death or lost to follow-up , whichever occurs first)..

To ensure consistent and unbiased collection of effectiveness endpoints, the concepts of scheduled study visits, post-treatment follow-up, and long-term surveillance are clearly distinguished.

Scheduled study visits refer to predefined documentation timepoints during active treatment with Lorlatinib, based exclusively on data generated in routine clinical practice. These visits do not represent protocol-mandated interventions.

End of Treatment (EOT) is defined as the date of permanent discontinuation of Lorlatinib, irrespective of the reason (e.g. disease progression, toxicity, patient decision). If permanent discontinuation occurs prior to the last scheduled visit, an EOT documentation will be performed using information available from routine clinical records.

Following EOT, patients will remain under treatment-independent follow-up for effectiveness endpoints. Collection of progression-free survival (PFS), time to next treatment (TTNT), overall survival (OS), PFS2, and subsequent anticancer therapies will continue until end of study, death, withdrawal of consent, or loss to follow-up. This approach ensures that data from early progressors and patients discontinuing Lorlatinib due to toxicity are fully captured and not systematically lost.

Patient-reported outcomes (QoL and work productivity) will be collected only in patients who remain on Lorlatinib treatment and have a valid baseline assessment. After permanent discontinuation of Lorlatinib (EOT), no further QoL or PRO questionnaires will be administered.

Long-term surveillance refers to ongoing collection of survival status and subsequent treatment information after completion of scheduled visits and/or after EOT, without predefined visit windows and without any study-specific procedures.

Study Visits

The study will be conducted, according to clinical practice:

- **Baseline visit:** the day on which the patient fulfils the inclusion and exclusion criteria including signature of the Informed Consent (i.e. the day on which the prospective observation starts) (within 60 days of Lorlatinib treatment start)
- **Visit**-1: data collection visit at month 4 of Lorlatinib
- **Visit 2:** data collection visit at month 7 of Lorlatinib
- **Visit 3**:data collection visit at month 13 of Lorlatinib
- **Visit** 4: data collection visit at month 19 of Lorlatinib, will be the final study visit for a patient..
- After the fourth study visit at month 19, further follow up will be done every six months. This will include: PFS and Lorlatinib treatment.
- **End Of Study (EOS)**: end of data collection (end of data collection expected 01 January 2030)

Table 2 Data collection overview

Study Visits and Assessments	Baseline	Scheduled Visits *	Visit 1	Visit 2	Visit 3	Visit 4		End Of Treatment (EOT) Or Final	Post EOT follow up	End Of Study (EOS)
Informed consent	X									
SOCIO DEMOGRAPHIC DATA										
Medical history	X									
Physical examination including Height and weight	X	X	X	X	X	X		X		
Previous personal and family history of cancer	X									
CLINICAL DATA										
ECOG PS	X	X	X	X	X	X		X		
Laboratory: Hematology and Blood chemistry (lipid profile included). According to routine clinical practice	X	X	X	X	X	X		X		
Comorbidities since Index Date: Charlson Index	X									
Concomitant treatment(s) including previous history of treatment of Thromboembolic Disease	X	X	X	X	X	X		X		
Information of baseline tumor diagnosis: date, staging with TNM (tumor nodes metastasis) classification, biopsy, programmed cell death ligand 1 (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) or other anti-cancer treatments	X									
Assessments of computer tomography (CT) scan	X	X						X (if available)	X (if available)	

Study Visits and Assessments	Baseline	Scheduled Visits *	Visit 1	Visit 2	Visit 3	Visit 4		End Of Treatment (EOT) Or Final	Post EOT follow up	End Of Study (EOS)
Assessments of brain magnetic resonance imaging (MRI)	X	X						X (if available)	X (if available)	
LORLATINIB TREATMENT										
Lorlatinib treatment status: Start, Stop, and Discontinuation date	X	X	X	X	X	X		X	X	X
Dose by cycle	X	X	X	X	X	X		X	X	X
Reason for discontinuation or for dose reduction	X	X	X	X	X	X		X	X	X
Evaluation of Treatment Response: method (CT scan, MRI, others) and results		X	X	X	X	X		X	X (if available	X (if available
AFTER LORLATINIB TREATMENT										
Time-to-event endpoints (PFS, TTNT, PFS2, OS)								X	X	X
Date of death or last follow-up or last contact (Survival Status)								X	X	X
Subsequent anticancer therapies								X	X	X
QUALITY OF LIFE										
EORTC QLQ-C30(2) and QLQ-LC13(3)	X	X	X	X	X	X		X (if available		
WORK PRODUCTIVITY										
WPAI:GH(4)	X	X			X	X		X		
SAFETY										
AEs/ SAE	X	X	X	X	X	X				

*Scheduled visits refer to documentation timepoints (see above) aligned with routine clinical practice during active Lorlatinib treatment. No visit windows or study -mandated procedures are defined.

9.2.1 Inclusion Criteria

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

1. Patients with histologically or cytologically confirmed diagnosis of locally advanced (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) ALK+ NSCLC according to Union for International Cancer Control (UICC) 9th edition(1) with determination of ALK status by local and approved diagnostic test. Refer to section 8. Research question and objectives.

2. Patients aged ≥18 (male or female) at inclusion who have initiated first-line therapy with Lorlatinib up to 60 days prior to enrollment in the study according to routine clinical practice. In some special cases, enrolment is possible after 60 days.

3. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

4. Eastern Cooperative Oncology Group Performance Status ECOG PS 0-2.

9.2.2 Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

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

9.3 Variables

Variable	Role	Data Source(s)	Operational Definition
Safety			
1) AEs, SAEs;	Outcome measures	Investigators, clinical patient record (CPR)/ Electronic Health record (EHR)	• Time to onset and duration of AEs • According to CTCAE v6(1): 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

Variable	Role	Data Source(s)	Operational Definition
			conduct normal life functions) • Results in congenital anomaly/birth defect
2) non-serious AEs (as applicable) and scenarios involving:	Outcome measures	Investigators, clinical patient record (CPR)/ Electronic Health record (EHR)	• An AE is any untoward medical occurrence in a patient administered to a medicinal product. • Time to onset and duration of AEs and frequency • According to CTCAE v6(1)
3) exposure during breast feeding, medication error, overdose, misuse, lack of efficacy,			
4) exposure during pregnancy (EDP),			
5) occupational/ environmental exposure			
6) non-serious AEs (as applicable)			• non-serious AEs (as applicable)
7) AESI	Outcome measures	Investigators, clinical patient record (CPR)/ Electronic Health record (EHR)	• AESI: AV block, pancreatitis • Time to onset and duration of AEs and frequency • According to CTCAE v6(1)
Effectiveness			
PFS	Outcome measures	Investigators, CPR / EHR, CT or MRI	Time from initiation of first-line Lorlatinib to the first occurrence of disease progression or death from any cause
TTNT	Outcome measures	Investigators, CPR / EHR, CT or MRI	Time from date of treatment initiation to date of next line treatment or death, whichever comes first
ORR	Outcome measures	Investigators, CPR / EHR, CT or MRI	Percentage of participants with a CR or PR as a best response during the Lorlatinib treatment. Responses to treatment will be defined according to physician

Variable	Role	Data Source(s)	Operational Definition
DOR	Outcome measures	Investigators, CPR / EHR, CT or MRI	Duration from the onset of the first Lorlatinib tumor response to disease progression or death for any reason
DCR	Outcome measures	Investigators, CPR / EHR, CT or MRI	Percentage of patients with CR, PR, or SD at least for 3 months to Lorlatinib evaluated by physician
IC-RR	Outcome measures	Investigators, CPR / EHR	Proportion of participants with an intracranial CR or PR as response during the Lorlatinib treatment. Responses to treatment will be defined according to physician
IC-TTP	Outcome measures	Investigators, CPR / EHR	Time from date of diagnosis or treatment initiation until intracranial progression or death.
Duration of IC Response	Outcome measures	Investigators, CPR / EHR	The length of time that a tumor continues to respond to treatment at intracranial level without the cancer growing or spreading at extracranial level or death
DOT	Outcome measures	Investigators, CPR /EHR	Time between the initiation of Lorlatinib and last dose of Lorlatinib
Cumulative incidence of BM at 12 and 18 months (in patients' population with and without baseline BM)	Outcome measures	Investigators, CPR / EHR, CT or MRI	Cumulative incidence of BM at 12 and 18 months in-population with and without baseline BM
Time to brain radiation for patients with BM at baseline from start of lorlatinib treatment	Outcome measures	Investigators, CPR / EHR	Time to whole brain irradiation or to stereotactic radiation
Time to brain radiation for patients without BM at baseline from start of lorlatinib treatment	Outcome measures	Investigators, CPR/ EHR	Time to whole brain irradiation or to stereotactic radiation
Proportion of participants with extracranial progression and sites of progression, assessed by the treating physician	Outcome measures	Investigators, CPR / EHR, CT or MRI	• Extracranial progression Yes/No, • Sites of (extracranial) progression: 1-3 sites; 4-6 sites or No
Proportion of participants with oligoprogression (3-5 metastasis) and sites of progression, assessed	Outcome measures	Investigators, CPR / EHR, CT or MRI	• Oligoprogression Yes/No • Sites of progression

Variable	Role	Data Source(s)	Operational Definition
by the treating physician			
OS	Outcome measures	Investigators, CPR / EHR	OS rate at 24 months since the aNSCLC diagnosis. OS rate at 24 months since the Lorlatinib first dose.
PFS subsequent line after Lorlatinib failure (PFS2)	Outcome measures	Investigators, CPR / EHR	Time from initiation of first subsequent line after Lorlatinib to the first occurrence of disease progression or death for any cause
ORR subsequent line after Lorlatinib failure	Outcome measures	Investigators, CPR / EHR	Proportion of participants with a CR or PR as a best response during the first subsequent line after Lorlatinib failure. Responses to treatment will be defined according to physician evaluation
DOT subsequent line after Lorlatinib failure	Outcome measures	Investigators, CPR / EHR	Time between the initiation of the first subsequent line after Lorlatinib failure to the last dose of that treatment.
Socio-demographic data/ Patient's characteristics/Disease characteristics			
Age at the treatment initiation	Baseline patients' characteristics	Investigators, CPR / EHR	Time in years between birth date and date of Lorlatinib initiation
Gender	Baseline patients' characteristics	Investigators, CPR / EHR	• Male/female/Undifferentiated
Height at treatment initiation	Baseline patients' characteristics	Investigators, CPR / EHR	• Meters
Weight at treatment initiation (and usual weight prior to diagnosis)	Baseline patients' characteristics	Investigators, CPR / EHR	• Kilograms
Smoking Status	Baseline patients' characteristics	Investigators, CPR / EHR	• Current smoker/ former smoker/ never smoker/ occasional smoker/unknown
Histological classification	Baseline patients' characteristics	Investigators, CPR / EHR	• Non-squamous/ squamous/ large cell NSCLC/ unknown
Date at diagnosis	Baseline patients' characteristics	Investigators, CPR / EHR	• DDMMYYYY
Presence of BM at baseline	Baseline patients' characteristics	Investigators, CPR / EHR	• Yes/No/Unknown

Variable	Role	Data Source(s)	Operational Definition
Patient's clinical situation before the start of treatment Lorlatinib by ECOG PS	Baseline patients' characteristics	Investigators, CPR / EHR	• Baseline autonomy status of the patient by ECOG
Localization and number of metastatic sites at diagnosis	Baseline patients' characteristics	Investigators, CPR / EHR	• Single Metastasis/ Oligometastatis/ Polymetastasis/ Diffuse Metastasis
Medical history			
Comorbidities	Baseline patients' characteristics	Investigators, CPR / EHR	• Depression Yes/ No • Psychiatric disease Yes/No • Neurocognitive disease Yes/No • Cardiovascular Yes/No • Diabetes Yes/No • Hyperlipidemia Yes/No
Baseline relevant comorbidities, Charlson Comorbidity Index	Baseline patients' characteristics	Investigators, CPR / EHR	• Relevant comorbidities Yes/ No • Lack of comorbidity: 0-1 • Low comorbidity: 2 • High comorbidity: ≥3
Relevant concurrent medications	Baseline patients' characteristics	Investigators, CPR / EHR	• Neurotropic, Psychiatric and mood medication • Anticonvulsants • Statins • Other
Description of ALK testing methods used in Italy	Baseline patients' characteristics	Investigators, CPR / EHR	• Immunohistochemistry (IHC)/ Fluorescence in situ hybridization (FISH)/ next generation sequencing (NGS)/ RNA sequencing/ NanoString/ others: specify
TAT of ALK-testing	Baseline patients' characteristics	Investigators, CPR / EHR	• Days/ from date of histology and date of ALK rearrangement report
ALK rearrangement	Baseline patients' characteristics	Investigators, CPR / EHR	• Yes
Clinical data prior to treatment initiation with Lorlatinib			
History of adjuvant/neoadjuvant treatment	Baseline patients' characteristics	Investigators, CPR / EHR	• Yes/No • Adjuvant/neoadjuvant • Radiotherapy Yes/No • Chemotherapy/ALK TKI • Surgery Yes/No
Clinical data during treatment with Lorlatinib			

Variable	Role	Data Source(s)	Operational Definition
Date of first administration of Lorlatinib	Baseline patients' characteristics	Investigators, CPR / EHR	• DDMMYYYY
Doses and duration of treatment with Lorlatinib	Outcome measures	Investigators, CPR / EHR	• Dosages 100 mg/ 75 mg/50 mg • Duration in Treatment in days
Permanent discontinuation and reason	Outcome measures	Investigators, CPR / EHR	• AEs/Physician's choice/ Patient's choice • Permanent discontinuation date
Temporary discontinuation and reason	Outcome measures	CPR / EHR	• Yes/No • Date of Start of discontinuation and date of recommencing of lorlatinib • Reason
Dose reduction and reason	Outcome measures	CPR / EHR	• From 100 mg to 75 mg • From 75 mg to 50 mg • Date of Start of reduction and date of next dose modification of lorlatinib (multiple modifications can be entered) • Reason
Description of subsequent treatment (chemotherapy or TKI) including type of regimen (chemotherapy or TKI)	Outcome measures	CPR / EHR	• ALK TKI/ chemotherapy with or without immunotherapy/ immuno-monotherapy/ other
Description of Co-Medication due to therapy management	Outcome Measures	CPR/ EHR	• Antihypertensive Yes/No • Anxiolytic/Sedative Yes/No • Antidepressant Yes/No • Anticoagulation Yes/No • Diuretic Yes/No • Antidiabetic drug Yes/No
QoL	Outcome measures	Electronic PRO	• EORTC QLQ-C30(2) and QLQ-LC13(3)- see section 9.6.3
Cost-effectiveness	Outcome measures	Electronic PRO	• WPAI:GH(4)
Clinical data after Lorlatinib completion			
Data collection of resistance testing (in	Outcome measures	CPR / EHR	• Method of testing (NGS/ liquid biopsy)

Variable	Role	Data Source(s)	Operational Definition
case of disease progression)			• ALK domain resistance mutation • ALK rearrangement loss • Bypass Lorlatinib resistance mutation • Free text in eCRF • NSCLC histological switch

Quality of Life Assessments

Assessments will be completed at the timepoints specified in "Table 2: Data Collection Overview"

Assessments will be completed by patients on each study visit:

- **EORTC QLQ-C30**: is a cancer-specific QLQ, 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/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).(2)
- **EORTC 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 QoL 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.(3)
- **WPAI:GH:** The Work Productivity and Activity Impairment – General Health (WPAI-GH) Questionnaire is a 6-item instrument to measure impairments over the past 7 days in both paid work and unpaid work due to one's health.(4)

9.4 Data Sources

All data collected in this study are intended to capture the real-world treatment patterns and outcomes of patients with ALK+ aNSCLC (for details on data collection refer to the table "data collection overview in section 10.2).

Data for this study will be collected prospectively during routine clinical visits and through patient-reported questionnaires. Information on demographics, clinical characteristics, treatment exposure, and relevant covariates will be recorded in a standardized electronic Case Report Form (CRF) only by the site staff authorized by the principal investigator.

- Patients' medical charts:

Patient medical charts will be used to record clinical and treatment data from patients' existing medical records into an eCRF following the patient's standard of care clinic visits. For the medical charts the validation is dependent on the validation strategies of each single study site.

- eCRF:

The information to evaluate the primary and secondary objectives of this study will be collected by means of eCRFs in the ACTide EDC [redacted]). The investigator and authorized study personnel, only after they have successfully completed the specific training and

learning test, can access this system via role-based permissions to enter and review patient data. The ACTide EDC system is validated according to GAMP 5 Category 4. (*What is GAMP®? | ISPE | International Society for Pharmaceutical Engineering*)

- Patient questionnaires(2-4):

The analysis of QoL patient questionnaires is part of the exploratory analyses of this study. Quality of life (QOL) and other -patient reported outcomes will be assessed using validated questionnaires (EORTC QLQ-C30, QLQ-LC13, WPAI, described below) that have been widely used in the target population. (*Wood R. et al Qual Life Res . 2019 Jul;28(7):1849-1861. doi: 10.1007/s11136-019-02152-6. Epub 2019 Mar 2.*)

For this purpose, the following validated PROs will be collected electronically, using personal devices of the patients in combination with the web-based electronic PRO (ePRO) tool [redacted] of the validation of the different QoL refer to the descriptions below and the respective cited publication):

1) 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 QoL. The remaining six single items evaluate additional cancer-associated symptoms and the perceived economic impact of the disease and treatment(2).

2) The QLQ-LC13 is a supplementary, lung cancer specific questionnaire with 13 items addressing symptoms associated with lung cancer and its standard treatment(3). Regarding EORTC QLQ-C30, Cocks et al. performed qualitative interview results from 113 patients with cancer from Europe and the United States 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 QoL in patients with localized-to-advanced cancer(19). consider 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 QLQ(3).

3) The productivity and activity impairment (WPAI) is a questionnaire with 6 items addressing the productivity of patients with health problems. It was established and validated as described by Reily et al.(4).

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. For monitoring activities and in case of inspection by the competent health authorities or internal audit of the sponsor, respectively the monitors, 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.

Personal data will be treated in accordance with all applicable regulations: according to the Regulation 2016/679 of the European Parliament and the Council of April 27th, 2016 on General Data Protection Regulation (GDPR). In Italy, it is regulated by the Legislative Decree 30 June 2003, n.196, "Personal Data Protection Code".

9.5 Study Size

This non-interventional study is descriptive in nature and is not designed to formally test statistical hypotheses or to demonstrate statistical superiority or non-inferiority.

The planned sample size of approximately 70-80 patients is based on feasibility considerations and is intended to provide a descriptive estimate of the progression-free survival (PFS) rate at 18 months under real-world clinical conditions in Italy.

The precision of the estimated PFS rate at 18 months will be described using two-sided 95% confidence intervals derived from Kaplan–Meier estimates. The calculation of confidence intervals serves solely to quantify the uncertainty of the descriptive survival estimates.

No formal power-based or event-driven sample size calculation was performed.

Estimates of PFS at later time points (e.g. 18 months) will be considered exploratory and interpreted with caution due to staggered patient accrual, administrative censoring, and decreasing numbers of patients at risk over time.

9.6 Data Management

[redacted]

All data in the context of this study will be collected, stored, and evaluated in accordance with regulatory requirements and applicable guidance for clinical records (also electronic records), including the GDPR.

All study data will be directly entered into eCRFs. Participating physicians will not have access to the data entered by other participating physicians. All patient-level data will be entered in a pseudonymized manner to prevent direct or indirect patient identification, including any personal information, together with any other information (such as physician details) that may reveal patient identity.

Data from the eCRFs will be compiled by the investigational site medical staff into a single, pseudonymized dataset. The data management process is scheduled to include the following steps:

- Compilation of all data into a single pseudonymized dataset
- Data cleaning: this will be by the delegated CRO Data management Team. Both automated and manual checks will be performed.

The delegated CRO will perform checks to support the participating physicians in the data entry to assess the appropriateness and consistency of data entered in the eCRF system. These checks will be implemented as warnings, i.e., in case of data entry error, an alert appears, inviting to make a correction. The participating physician will have the option to correct data or to ignore the warning. Checks on exported data will be run in order to verify that no inconsistent data are entered in the eCRF. A few automated checks will be performed on the data before and after the Source Data Verification (SDV) by Data Manager (DaM) using software (SAS) while other checks will be performed manually by DaM/Clinical Research Associate (CRA). The consistency with source data will be assessed through

Source Data Verification during the monitoring visits. Checks on exported data will be run in order to verify that no inconsistent data are entered in the eCRF.

Details about the Source Data Verification process will be provided in the Monitoring Plan.

- Construction of the observational research file

The study data flow can be described as follows: after the study physician reports the required information in the eCRF, all data will be transferred by a secure web-interface in a pseudonymized manner to the central database. The delegated CRO will supervise the collection of the data described above from the participating hospitals, support investigators for data queries resolution as needed, and perform quality checks prior to database lock and subsequent analysis.

For electronic data capturing and data management of this study, the web-based validated software (ACTide system) will be employed.
The participating physician agrees to provide, upon request, all necessary background information regarding his/her documentation. The participating physician ensures that the documented information is recorded correctly.

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 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, initialled, 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.

ePRO data collected via [redacted] system are stored centrally in encrypted form with controlled access managed [redacted] as the system provider.

A document should be available at the investigator site and at Pfizer that clearly identifies source data location and any additional records maintained at the investigator site that might also act as supportive documentation

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent 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 (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study. [redacted] have expressly agreed to a different period of retention via a separate written agreement.

Records must be retained for longer than 15 years if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.6.3 Management of Patient Questionnaires

The validated and widely used EORTC QLQ-C30, QLQ-LC13 and WPAI:GH questionnaires will be used to document patients' quality of life. Patients are asked to complete the questionnaires at baseline study visits and additional timepoints (please refer to table 2 "data collection overview" in section 9.2).

The web-based electronic PRO (ePRO) tool from ACTide System will be used to document the EORTC QLQ-C30, QLQ-LC13 and WPAI:GH questionnaires.

For the site:

The ePRO will be accessed on any device, using the patient's own smartphone, tablet, or computer. To use ePRO, the investigator will be asked to enter the patient's email address into the eCRF and trigger a message. The patient then will receive an email with a secure link to personal ACTide ePRO page. A personal password will be set by the patient at first login. Same link and password can then be used by the patient for all subsequent completions.
If necessary, automatic reminders for questionnaires completion (via email) can be scheduled at predefined times, according to the protocol schedule. Patient-reported data will be instantly captured into the eCRF, providing investigators with timely and accurate insights into patients' experiences. The capture system is a validated process that will assure data integrity and correctness.
Validated electronic versions of the questionnaires, in local language, will be used.
The eCRF data related to questionnaires will be checked for completeness by the CRA/Data Manager of the CRO and considered as source data, as no paper, hand-written questionnaires will be available.

9.7. Data Analysis

9.7.1. Statistical Methods

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.

No formal hypotheses will be tested. Analyses will be performed with all available data; no imputation for missing data will be conducted.

Questionnaires will be evaluated according to their respective user manuals.

For continuous variables the number of non-missing observations, mean, standard deviation, minimum, 25th percentile, median, 75th percentile and maximum will be presented. For categorical variables absolute and relative frequencies will be provided.

The Kaplan-Meier method will be used for time-to-event analyses (PFS, TTNT, DOR, duration of intracranial response, time to brain irradiation, DOT, PFS2, OS, DOT and PFS of subsequent lines of treatment), including the primary endpoints PFS and TTNT. Time-to-event variables will be presented with survival rates at specified time points, lower quartile, median, upper quartile and the respective 95% confidence limits. Frequency of the number of events will be given, and a Kaplan-Meier plot will be provided.

9.7.2. Primary and Secondary Endpoint Analysis

Analyses of primary and secondary endpoints will be conducted on the basis of the Full Analysis Set as described in section 9.7.3. below.

To account for potential confounders, such as the presence of brain metastases at baseline and prior exposure to a second-generation ALK TKI, subgroup analyses will be performed with stratifications by potential confounders. Analyses of subgroups will be detailed in the SAP.

Further sensitivity analyses may be specified in the SAP if deemed necessary.

9.7.3. Analysis Populations

Full Analysis Set (FAS): The FAS consists of all enrolled patients having received at least one dose of Lorlatinib. Patients treated off-label or violating any inclusion/exclusion criteria detected after start of treatment will be excluded. FAS is the relevant analysis population for all analyses but QoL.

Safety Analysis Set (SAS): The Safety Analysis Set consists of all enrolled patients having received at least one dose of Lorlatinib, including violator patients (i.e. patients treated off-label or violating any inclusion/exclusion criteria).

PRO set: The PRO set includes all patients of the FAS with signed written informed consent at/before start of Lorlatinib treatment (prospective enrollment). QoL analyses will be performed on the PRO set.

An overview of the planned analyses for each endpoint is provided in Table 3

Table 3 Summary of Endpoints, Analysis Populations, and Methods

Endpoint	Analysis Population	Statistical Method / Summary
Primary Endpoints		
PFS rate at 18 months	Full Analysis Set	Kaplan–Meier estimate; two-sided 95% CI using log(–log) transformation and Greenwood's variance
Time to Next Treatment (TTNT)	Full Analysis Set	Kaplan–Meier estimate; median and time-specific rates with two-sided 95% CI
Secondary Effectiveness Endpoints		
Objective Response Rate (ORR)	Full Analysis Set	Proportion with exact two-sided 95% CI (Clopper–Pearson)

Endpoint	Analysis Population	Statistical Method / Summary
Disease Control Rate (DCR)	Full Analysis Set	Proportion with exact two-sided 95% CI (Clopper–Pearson)
Duration of Response (DOR)	Responders in Effectiveness Analysis Set	Kaplan–Meier estimate; median and 95% CI
Intracranial response rate (IC-RR)	Patients with baseline brain metastases	Proportion with exact two-sided 95% CI (Clopper–Pearson)
Duration of intracranial response	Patients with intracranial response	Kaplan–Meier estimate
Intracranial Time to Progression (IC-TTP)	Patients with baseline brain metastases	Kaplan–Meier estimate
Time to brain irradiation	Full Analysis Set	Kaplan–Meier estimate
Duration of Treatment (DOT)	Full Analysis Set	Kaplan–Meier estimate
Progression-Free Survival 2 (PFS2)	Full Analysis Set	Kaplan–Meier estimate
Overall Survival (OS)	Full Analysis Set	Kaplan–Meier estimate; median and 95% CI
Cumulative incidence of brain metastases	Patients with and without baseline brain metastases	Descriptive Kaplan–Meier estimates at 12 and 18 months
Safety Endpoints		
All AEs, TRAEs, SAEs	Safety Analysis Set	Frequency and percentage by SOC and PT
Adverse events of special interest (AESIs)	Safety Analysis Set	Frequency and percentage by SOC and PT
Dose modifications and discontinuations	Safety Analysis Set	Frequency and percentage
Exploratory Endpoints (QoL)		
EORTC QLQ-C30 and QLQ-LC13 scores	PRO Analysis Set	Descriptive statistics of observed scores and change from baseline
WPAI:GH scores	PRO Analysis Set	Descriptive statistics of observed scores and change from baseline

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 monitoring visit by the person appointed by the sponsor and a review by the IEC and/or inspections/quality assurance audits conducted respectively by the relevant regulatory authorities and the study sponsor.

The EDC includes online validation of eCRFs during data capturing, e.g., automatic range checks, plausibility, typing errors. In addition to system-based plausibility checks, a formal query process will be implemented to resolve inconsistencies in documented data.

The sponsor will be responsible for the quality control of the study. Quality control checks will be delegated to the vendor to ensure data quality and the safe storage of data and reports. The scope of these checks for the eCRFs and the clinical database will focus on the study objectives and will be defined in the Data Management Plan (DMP). All quality check findings and actions taken will be documented.

Analyses are programmed according to the specifications in the protocol and in the SAP. Quality assurance of statistical analyses is ensured through a comprehensive version control system using Git and GitLab, which guarantees complete traceability and reproducibility of all analytical processes. All analyses are performed in SAS. Details for quality checks for the analysis, result tables and reports will be described in the Analysis and Reporting Plan (ARP). The security and safety of collected data will be ensured by data storage on secure servers where files will be accessible only to the appointed vendor study team members.

The study will be conducted in compliance with this protocol. Study personnel meetings, training and standard operation procedures (SOPs) will be carried out during the study life cycle to ensure appropriate study conduct. Study personnel involved in study conduct and data management will be qualified by education, training, and experience to perform their respective task(s).

9.9. Limitations of the Research Methods

This observational, noninterventional PASS is subject to inherent limitations of observational research such as confounding and selection bias, as treatment decisions are made according to routine clinical practice rather than through randomization. (23) Despite comprehensive prospective collection of baseline and clinical variables, residual confounding cannot be fully excluded. Effectiveness endpoints, including real-world progression free survival, will be assessed by treating physicians without blinded independent central review, which may introduce variability across sites.

Data will be derived from routine medical records and patient reported outcomes, and therefore incomplete or missing data is expected, particularly for variables not routinely assessed in all centers. Exploratory data elements, such as resistance testing, are collected only if performed as part of standard clinical practice, which may limit completeness and comparability.(21-22)

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.

Data collected in this study will reflect clinical practice in Italy. 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 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

Not applicable.

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 Vendor and 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.

Pediatric assent language is not applicable due the inclusion criteria of the study.

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 IRB/IEC 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.

Investigators can follow their site's normal practice for documenting that the person signing the informed consent document is the patient's legally acceptable representative, but the source records should describe how it was determined. Caregivers for adults would normally be expected to have paperwork documenting their legal authority to make decisions on behalf of another adult.

The investigator, or a person designated by the investigator, will obtain written informed consent and privacy consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent documents.

It may be appropriate or necessary to include additional justification or criteria for determining when consent may be provided by a legally acceptable representative, particularly if not all patients in the study will require a legally acceptable representative. If consenting patients may progress to decisional impairment during the course of a study, include provisions for determining when consent from a legally acceptable representative will become necessary and how it will be obtained. If patients lacking the decisional capacity to provide consent or assent at the start of the study could be expected to gain that capacity during the study, include provisions for determining when the patient's consent or assent should be obtained for him or her to continue in the study.

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.

10.4. Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, (eg, recruitment advertisements, if applicable) from the relevant IRB/IEC. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.5. Ethical Conduct of the Study

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. In accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society of Pharmacoepidemiology (ISPE), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making, International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology and the GDPR. (25-29)

The study personnel involved in conducting this study 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, 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 and approved by the IEC/IRB before implementation”

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

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Requirements

Table 4 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, 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 4 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	AV block, pancreatitis
Scenarios involving exposure during breastfeeding, medication error, overdose, misuse, 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 4 **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 4 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 4 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.

[redacted]

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 4) 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 (e.g., patient changes his/her mind about participation, patient failed screening criteria), 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
- 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

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

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute 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 (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

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

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (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 4.

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 4 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 (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow-up to the initial EDP report.
- In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth.
- In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

Additional information about pregnancy outcomes that are reported as SAEs:

- 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 (e.g., follow-up on preterm infants to identify developmental delays).

Exposure during breastfeeding

Exposure during breastfeeding (EDB) is reportable using the non-interventional study AEM Report form, irrespective of whether a safety event has occurred. The procedures for reporting as per Table 4 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 4 and irrespective of the presence of an associated safety event. Since the information about the occupational and environmental exposure does not pertain to a participant enrolled in the study, the information is not recorded on CRF; however, a copy of the completed non-interventional study SAE Report Form must be maintained in the investigator site file.

Below are examples of environmental/occupational exposure:

- A nonparticipant (a family member or a healthcare professional (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 (e.g., 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 (e.g., female family member or female HCP) is found to be pregnant or breastfeeding while being exposed or having been exposed to Lorlatinib (i.e., 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 (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer)
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer DSU within the timelines outlined in Table 4, 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 (e.g., potential medication errors or near misses).

When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

- An identifiable reporter
- A suspect product
- The event medication error.

Overdose, Misuse,

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 4.

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 4.

11.1 Single Reference Safety Document

The Summary of product characteristics (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 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 (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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.

Registration of the study in the EU PAS register is mandatory.

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14. LIST OF TABLES

15. LIST OF FIGURES

Not applicable.

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCEPP checklist for the study protocol is available as a stand-alone document.

18. ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

Document Approval Record

Document Name:	B7461061_NIS PASS Study Protocol_Completed Review NISRC-O_V 1.1_19May2026
Document Title:	B7461061_NIS PASS Study Protocol_Completed Review NISRC-O_V 1.1_19May2026

Signed By:	Date(GMT)	Signing Capacity
Rubino, Heather	20-May-2026 11:55:49	Final Approval
Masi, Maria Claudia	20-May-2026 18:00:58	Manager Approval