TITLE PAGE

Protocol Title: Single-Arm Study of Lorlatinib in Participants with Anaplastic Lymphoma Kinase (ALK)-Positive Non-Small Cell Lung Cancer (NSCLC) Whose Disease Progressed After One Prior Second-Generation ALK Tyrosine Kinase Inhibitor (TKI)

Protocol Number: B7461027

Amendment Number: Not applicable

Compound Number: PF-06463922

Study Phase: Phase 4

Short Title: Study of Lorlatinib In Participants with Anaplastic Lymphoma Kinase (ALK) -Positive NSCLC

Acronym: Not Applicable

Sponsor Name: Pfizer, Inc

Legal Registered Address: 235 East 42nd Street, New York, NY 10017-5755, USA

Regulatory Agency Identifier Number(s)

Registry	ID
IND	118,296
EudraCT	2019-002504-41

Approval Date: 22 January 2020

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	22 Jan 2020

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: Single-Arm Study of Lorlatinib in Participants with Anaplastic Lymphoma Kinase (ALK)-Positive Non-Small Cell Lung Cancer (NSCLC) Whose Disease Progressed After One Prior Second-Generation ALK Tyrosine Kinase Inhibitor (TKI)

Short Title: Study of Lorlatinib In Participants with Anaplastic Lymphoma Kinase (ALK) -Positive NSCLC

Rationale:
On the basis of pivotal Phase 1/2 study B7461001, lorlatinib received Conditional Marketing Authorization (CMA) by the European Medicine Agency (EMA) on 7 May 2019 for the treatment of patients with ALK-positive metastatic non-small-cell lung cancer whose disease has progressed after:

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
- crizotinib and at least one other ALK inhibitor.

However, in view of the limited sample size of 28 patients post second generation ALK TKI from the pivotal phase 1/2 study B7461001, in addition to the ongoing Phase 3 study B7461006 (CROWN), the EMA requested a post-authorization efficacy study (PAES) to obtain additional data on the activity of lorlatinib in the second-line setting.

Objectives, Estimands and Endpoints

Objectives	Estimands	Endpoints
Primary		
• To assess Overall and Intracranial Response Rate of single-agent lorlatinib in participants with advanced ALK-positive NSCLC whose disease has progressed on alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy	• The primary estimand is the treatment effect of lorlatinib by independent central review (ICR) from time of first dose until progression is met or subsequent anti-cancer therapy is administered for all participants who receive at least one dose of lorlatinib without regard to discontinuation from treatment	• Confirmed Objective Tumor Response assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 per ICR
Secondary		

• To assess secondary measures of clinical efficacy	• The estimand for Objective Response (OR) by investigator (INV) follows the estimand specified for the primary endpoint except that the treatment effect is based on INV • The estimand for Intracranial (IC) response is the Intracranial treatment effect (ie in brain lesions) of lorlatinib from time of first dose until Intracranial progression is met or subsequent anti-cancer therapy is administered for all participants who receive at least one dose of lorlatinib without regard to discontinuation from treatment • The estimand for Time to Tumor Response (TTR) is the treatment effect from the time of first dose to the first date of response that is subsequently confirmed for responders to lorlatinib • The estimand for Duration of Response (DOR) is the treatment effect from the first date of OR that is subsequently confirmed for responders to lorlatinib until progression or death, without regard to discontinuation from	• Every endpoint assessed by RECIST version 1.1 • Confirmed Objective Tumor Response assessed by INV • Confirmed Intracranial tumor response assessed per ICR and INV • TTR per ICR and INV • DOR per ICR and INV • Duration of Intracranial response (IC-DOR) per ICR and INV • TTP per ICR and INV • PFS per ICR and INV

	treatment unless new anti-cancer therapy is initiated or extended gap in tumor assessment is present prior to progression or death • The estimand for IC-DOR follows the estimand specified for the DOR, but limited to intracranial lesions • The estimand for Time to Tumor Progression (TTP) is the treatment effect from the time of first dose for all participants who receive at least one dose of lorlatinib until progression, without regard to discontinuation from treatment unless participant dies, new anti-cancer therapy is initiated or extended gap in tumor assessment is present prior to progression • The estimand for Progression Free Survival (PFS) is the treatment effect from the time of first dose for all participants who receive at least one dose of lorlatinib until progression or death, without regard to discontinuation from treatment unless new anti-cancer therapy is initiated or an extended gap in tumor assessment	

	is present prior to progression or death	
• To confirm the safety and tolerability of lorlatinib	• The estimand for safety is the incidence of Adverse Events from the time of first dose to 28 days post last dosing date or the date of initiation of a new anti-cancer therapy for all participants who receive at least one dose of lorlatinib	• Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.03), seriousness, and relationship to study therapy

Overall Design:
This is a Phase 4 open-label, multi center, multi-national, non-randomized, prospective, single-arm study of lorlatinib in adult participants with ALK-positive NSCLC who progressed on alectinib or ceritinib as first line of treatment for metastatic disease.

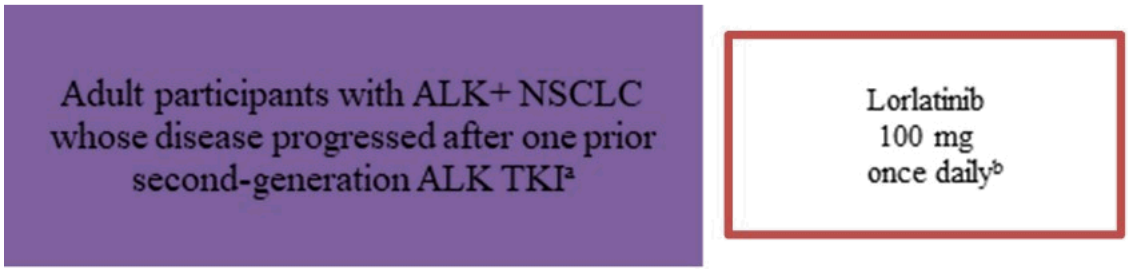
Disclosure Statement:
This is a Single Group Treatment study with 1 Arm that has No masking.

Number of Participants:
Approximately 85 participants will be screened to achieve 70 participants assigned to study intervention.

Intervention Groups and Duration:
Participants will take lorlatinib at the approved dose of 100 mg QD (once daily). Participants will be treated until disease progression, participant refusal/lost to follow-up, or unacceptable toxicity.

Data Monitoring Committee: No

1.2. Schema



a alectinib or certinib
b Treatment until disease progression, patient refusal/lost to follow-up, or unacceptable toxicity.

1.3. Schedule of Activities (SoA)

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to Section 8 of the protocol for detailed information on each assessment required for compliance with the protocol.

The Investigator may schedule visits (unplanned visits) in addition to those listed in the schedule of activities table in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Screening and Cycle 1

Visit Identifier	Screening*	Cycle 1 (21 days)	Notes *to be obtained within 28 days prior to registration
Visit Window	**≤28 days**	**Day 1 (±1 day)**	(X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required.
Informed consent	X		Must be obtained prior to undergoing any study specific procedures that are not considered standard of care.
Tumor history	X		
Medical history	X		Data on prior anti-cancer therapy will be collected along with the best-known response from the previous ALK inhibitor.
Physical examination	X	X	
Weight	X	X	
Performance Status	X	X	
Contraception check (as appropriate)		X	
Laboratory			
Hematology	X	(X)	No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. For those visits after C1D1, hematology labs should be performed according to lorlatinib product information.

Visit Identifier	Screening*	Cycle 1 (21 days)	Notes *to be obtained within 28 days prior to registration
Visit Window	**≤28 days**	**Day 1 (±1 day)**	(X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required.
Blood Chemistry	X	(X)	No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. For those visits after C1D1, blood chemistry should be performed according to lorlatinib product information.
Pregnancy test	X	(X)	For female participants of childbearing potential, a serum or urine pregnancy test will be performed once at the start of screening and once at the baseline visit, immediately before study intervention administration. The pregnancy test should be performed at the clinical site's local laboratory.
Cardiac Monitoring			
12-lead ECG	X	(X)	No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date. During study treatment additional triplicate ECGs may be performed as clinically indicated and according to lorlatinib product information.
LVEF Assessment	X		Echocardiogram or MUGA will be performed. During study treatment additional assessments may be performed as clinically indicated and according to lorlatinib product information. For France and Germany, a transthoracic echocardiogram (TTE) will be performed every 6 months (± 2 weeks) during treatment, and only at the end of treatment visit if the previous assessment was > 1 month. Pulmonary arterial pressure (PAP) will be assessed.
Registration			
Registration		(X)	Registration will be within 2 days prior to study treatment start.
Tumor Assessments			
CT and MRI Scan or Equivalent	X		Tumor assessments will include all known or suspected disease sites. CT or MRI scans of Chest Abdomen Pelvis [CAP] and MRI of the brain will be performed at screening. Bone scans (or bone MRI if preferred by investigator) will be performed at baseline for all participants and repeated every 12 weeks on study only if evidence of bone metastases is observed at baseline.

Visit Identifier	Screening*	Cycle 1 (21 days)	Notes *to be obtained within 28 days prior to registration
Visit Window	**≤28 days**	**Day 1 (±1 day)**	(X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required.
Cerebrospinal fluid if leptomeningeal/carcinomatous meningitis [LM/CM] disease is present	X		CSF is mandatory for participants who have asymptomatic radiologically suspected leptomeningeal disease (LM) or carcinomatous meningitis (CM) but negative spinal fluid.
Other Clinical Assessments			
Adverse Events	X	X	For AEs and SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study through and including a minimum of 28 calendar days after the last administration of the study intervention. Refer to Section 8.3.1 for all specifications.
Concomitant medications and non-drug supportive interventions	X	X	

1.3.2. Visits on Day 1 of Every Other Cycle (up to 35 cycles and >35 cycles)

Visit Identifier	Visits on Day 1 of Every Other Cycle up to 35 cycles (up to 24 months)	Visits on Day 1 of Every Other Cycle (> 35 cycles or 24 months)	Notes (X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required.
Visit Window	**±4 days**	**±4 days**	
Physical examination	X		
Weight	X		
Contraception check (as appropriate)	X (every cycle ±2 days)	X (every cycle ±2 days)	At cycle not requiring site visit the participant may be contacted by phone to confirm contraception is still appropriate per the protocol.
Laboratory			

Visit Identifier	Visits on Day 1 of Every Other Cycle up to 35 cycles (up to 24 months)	Visits on Day 1 of Every Other Cycle (> 35 cycles or 24 months)	Notes (X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required.
Visit Window	**±4 days**	**±4 days**	
Pregnancy test	X (every cycle ±2 days)	X (every cycle ±2 days)	Pregnancy tests will be routinely repeated at every cycle (±2 days) during the active treatment period and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. The pregnancy test should be performed at the clinical site's local laboratory. Where that is not possible, participants will provide the laboratory test results carried out at a non-clinical site laboratory, eg, by telephone, and bring a copy of the laboratory test results at the next cycle visit. The copy of the laboratory test results must be retained in the participants' file at the clinical site for documentation purposes.
Study Intervention			
Study Intervention	Once a day continuously		
Tumor Assessments			
CT and MRI Scan or Equivalent	(every 6 weeks ± 1 week)	(As per local clinical practice)	CT and MRI scans to be done at every 6 weeks ±1 week up to approximately 24 months (cycle 35) and then as per local clinical practice.
Other Clinical Assessments			
Adverse Events	X	X	
Concomitant medications and non-drug supportive interventions	X		All concomitant medications and non-drug supportive interventions should be recorded in the CRF until the participant has completed 35 cycles of treatment (approximately 24 months). After cycle 35 the data will be reported in the medical chart, but not collected in the CRF.

1.3.3. End of Treatment and Follow-Up

End of Treatment Visit: Obtain these assessments if not completed in the last week (last 6 weeks for tumor assessments up to 24 months).

Follow up: At least 28 days, and no more than 35 days after discontinuation of treatment participants will return to undergo review for resolution of any treatment related toxicity. Participants continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Participants discontinuing treatment for reasons other than progression of disease will continue to perform tumor assessments until PD up to approximately 24 months (cycle 35).

Visit Identifier	End of Treatment	Follow-up	Notes (X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required.
Visit Window	**±2 days**	**±7 days**	
Physical examination	X		
Weight	X		
Contraception check (as appropriate)	X	X	The participant may be contacted by phone to confirm contraception is still appropriate per the protocol. Males and females of childbearing potential must be contacted after study intervention discontinuation to ensure that they continue to use appropriate contraception for at least 98 and 35 days, respectively, after the last dose of study intervention.
Laboratory			
Pregnancy test	X	X	The pregnancy test should be performed at the clinical site's local laboratory. Where that is not possible, participants will provide the laboratory test results carried out at a non-clinical site laboratory, eg, by telephone, and bring a copy of the laboratory test results at the next cycle visit. The copy of the laboratory test results must be retained in the participant's file at the clinical site for documentation purposes.
Tumor Assessments			

Visit Identifier	End of Treatment	Follow-up	Notes (X) refer to specific footnote when the measurement may be optional /repeat measurement might not be required.
Visit Window	**±2 days**	**±7 days**	
CT and MRI Scan or Equivalent	(X)		Tumor assessment should be repeated at the end of treatment if more than 6 weeks have passed since the last evaluation. Tumor assessment should not be repeated at the end of treatment if progression occurs when the participant has shifted to the local clinical practice.
Other Clinical Assessments			
Adverse Events	X	X	
Concomitant medications and non-drug supportive interventions	(X)		

Abbreviations: AE = adverse events; CAP = Chest abdomen pelvis; c; CNS = central nervous system; CT = computed tomography; CRF = case report form; CSF = cerebrospinal fluid; C1D1 = cycle 1 day 1; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; LM = leptomeningeal meningitis; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NCI CTCAE = National Cancer Institute common terminology criteria for adverse events; PD = progression of disease; RECIST = Response Evaluation Criteria in Solid Tumors; TTE = transthoracic echocardiogram

2. INTRODUCTION

Lung cancer is one of the most common cancers in the world (2.1 million new cases estimated in 2018), 12% of all new cancers world-wide.[1] Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer.

In 2007, two research groups independently reported the discovery of an NSCLC oncogenic fusion gene (echinoderm microtubule-associated protein-like 4 [EML4]-ALK) that combines portions of the EML4 gene and the anaplastic lymphoma kinase (ALK) gene.[2, 3] This fusion gene encodes for the cytoplasmic fusion protein EML4-ALK which upon dimerization, results in constitutive activation of the kinase domain of ALK. Approximately 3-5% of NSCLC is histologically defined as ALK+[4] and the vast majority of ALK fusion positive cases were observed in young, non-smoking patients with lung adenocarcinoma, and are rarely coincident with c-ROS oncogene-1 (ROS1), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), or Kirsten Rat Sarcoma (KRAS) mutations.[2] Rearrangements of ALK gene represent a clinically and molecularly distinct subtype that shows sensitivity to therapy with ALK tyrosine kinase inhibitors. Standard initial treatment for ALK-positive non-small-cell lung cancer includes first-line crizotinib and, more recently, first-line alectinib or ceritinib.

Although most participants with ALK-positive NSCLC derive substantial clinical benefit from crizotinib and the second generation ALK-TKIs alectinib and ceritinib[5-8], some participants will not respond to treatment (intrinsic resistance), and other participants who initially experience clinical benefit will later develop resistance (acquired resistance) or develop disease progression in the central nervous system (CNS).[9, 10]

Among patients whose disease has progressed on second-generation TKIs used either in the first- or second-line setting, chemotherapy and/or immunotherapy would be the fall back standard of care.

Outcomes with chemotherapy alone have been modest. In a randomized Phase 3 trial of ceritinib vs chemotherapy (docetaxel or pemetrexed) in patients with ALK-positive NSCLC who had been previously treated with chemotherapy and crizotinib, chemotherapy had an objective response rate (ORR) of 6.9% and median PFS of 1.6 months, as determined by blinded ICR. Chemotherapy also has a limited intracranial (IC) ORR even in a treatment-naïve setting. In a randomized Phase 3 study of first-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged NSCLC, the platinum doublet was reported to have an IC ORR by ICR of 21.2% (95% confidence interval [CI]: 11.1, 34.7).[5]

In addition to standard chemotherapy regimens and anti-vascular agents, immunotherapy is also indicated for the second-line treatment of patients with ALK positive NSCLC after failure of a first line ALK-TKI (atezolizumab[11]) or as monotherapy in patients whose tumors express PD-L1 with a ≥ 1% tumor proportion score (TPS) and who have received at least one prior chemotherapy regimen and a target therapy (pembrolizumab[12]).

Although, these treatments have shown very promising results[13, 14], few patients with ALK positive tumors were enrolled and conclusive results in this specific subpopulation are still warranted.

As outlined in Section 2.2, the third-generation ALK TKI lorlatinib offers a therapeutic option active in this setting.

2.1. Study Rationale

On the basis of pivotal Phase 1/2 B7461001, lorlatinib received CMA by the European Medicine Agency (EMA) on 7 May 2019 for the treatment of participants with ALK-positive metastatic non-small-cell lung cancer whose disease has progressed after:

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
- crizotinib and at least one other ALK inhibitor.

However, in view of the limited sample size of 28 participants post second generation ALK TKI from the pivotal phase 1/2 study B7461001, in addition to the ongoing Phase 3 study B7461006 (CROWN), the EMA requested a PAES to obtain additional data on the activity of lorlatinib in the second-line setting.

2.2. Background

Lorlatinib is a highly potent, selective third-generation tyrosine kinase inhibitor directed at the ALK and c-ros oncogene 1 (ROS1) kinases. Using structure-based drug design, this macrocyclic tyrosine kinase inhibitor was developed to retain potency against most known ALK resistance mutations and to penetrate the blood–brain barrier. Lorlatinib demonstrated marked antitumor activity in mice bearing tumor xenografts that express echinoderm microtubule-associated protein-like 4 (EML4) fusions with ALK variant 1 (v1), including ALK mutations L1196M, G1269A, G1202R, and I1171T. Two of these ALK mutants, G1202R and I1171T, are known to confer resistance to alectinib, brigatinib, ceritinib, and crizotinib. Lorlatinib was also capable of penetrating the blood-brain barrier and demonstrated activity in mice bearing orthotopic EML4-ALK or EML4-ALKL1196M brain tumor implants.

In the pivotal single-arm, multicenter Phase 2 study, treatment with lorlatinib showed clinically relevant response rates and duration of response in participants with ALK-positive non-small-cell lung cancer who had previously received at least 1 ALK tyrosine kinase inhibitor, including the second-generation drugs ceritinib and alectinib. In the cohort of participants previously treated with a second generation ALK-TKI, a high proportion of participants achieved an OR (12 [42.9%] of 28) and durable responses (median duration of response 5.6 months [95% CI 4.2–not reached]).

Substantial intracranial activity was also observed in these participants suffering from frequent brain metastases. The proportion of participants with objective intracranial response to lorlatinib was 66.7% in participants with at least one measurable brain lesion at baseline.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of lorlatinib may be found in the Summary of Product Characteristics (SmPC), which is the single reference safety document (SRSD) for this study.

3. OBJECTIVES, ESTIMANDS AND ENDPOINTS

Objectives	Estimands	Endpoints
Primary		
• To assess Overall and Intracranial Response Rate of single-agent lorlatinib in participants with advanced ALK-positive NSCLC whose disease has progressed on alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy	• The primary estimand is the treatment effect of lorlatinib by independent central review (ICR) from time of first dose until progression is met or subsequent anti-cancer therapy is administered for all participants who receive at least one dose of lorlatinib without regard to discontinuation from treatment	• Confirmed Objective Tumor Response assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 per ICR
Secondary		
• To assess secondary measures of clinical efficacy	• The estimand for Objective Response (OR) by investigator (INV) follows the estimand specified for the primary endpoint except that the treatment effect is based on INV • The estimand for Intracranial (IC) response is the Intracranial treatment effect (ie in brain lesions) of lorlatinib from time of first dose until Intracranial progression is met or subsequent anti-cancer therapy is administered for all participants who receive at least one dose of lorlatinib without regard to discontinuation from treatment	• Every endpoint assessed by RECIST version 1.1 • Confirmed Objective Tumor Response assessed by INV • Confirmed Intracranial tumor response assessed per ICR and INV • TTR per ICR and INV • DOR per ICR and INV • Duration of Intracranial response (IC-DOR) per ICR and INV • TTP per ICR and INV • PFS per ICR and INV

	• The estimand for Time to Tumor Response (TTR) is the treatment effect from the time of first dose to the first date of response that is subsequently confirmed for responders to lorlatinib • The estimand for Duration of Response (DOR) is the treatment effect from the first date of OR that is subsequently confirmed for responders to lorlatinib until progression or death, without regard to discontinuation from treatment unless new anti-cancer therapy is initiated or extended gap in tumor assessment is present prior to progression or death • The estimand for IC-DOR follows the estimand specified for the DOR, but limited to intracranial lesions • The estimand for Time to Tumor Progression (TTP) is the treatment effect from the time of first dose for all participants who receive at least one dose of lorlatinib until progression, without regard to discontinuation from treatment unless participant dies, new anti-cancer therapy is initiated or extended gap in tumor	

	assessment is present prior to progression • The estimand for Progression Free Survival (PFS) is the treatment effect from the time of first dose for all participants who receive at least one dose of lorlatinib until progression or death, without regard to discontinuation from treatment unless new anti-cancer therapy is initiated or an extended gap in tumor assessment is present prior to progression or death	
• To confirm the safety and tolerability of lorlatinib	• The estimand for safety is the incidence of Adverse Events from the time of first dose to 28 days post last dosing date or the date of initiation of a new anti-cancer therapy for all participants who receive at least one dose of lorlatinib	• Adverse Events as characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v.4.03), seriousness, and relationship to study therapy

This protocol will use an independent endpoint adjudication committee to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria (see Section 9.5.2).

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 4 open-label, multi-center, multi-national, non-randomized, prospective, single arm study of lorlatinib in adult participants with ALK-positive NSCLC who progressed on alectinib or ceritinib as first line of treatment for metastatic disease. Approximately 85 participants will be screened to achieve 70 participants assigned to study intervention.

Participants will take lorlatinib at the approved dose of 100 mg QD. Participants will be treated until disease progression per RECIST 1.1, participant refusal/lost to follow-up, or unacceptable toxicity.

4.2. Scientific Rationale for Study Design

The pivotal phase 1/2 study B7461001 has included 28 participants who have progressed after a second generation ALK inhibitors used as a first line treatment. In order to allow for a more precise estimation of the 95% confidence interval (CI) of the primary endpoint the proposed study increases the sample size in this population.

4.3. Justification for Dose

The dose of 100 mg QD is the approved dose based on the safety and efficacy data provided by the Phase 1 portion of pivotal study B7461001.

4.4. End of Study Definition

The End of Trial is defined as 12 calendar months after the "last patient first visit" (LPFV) date in the study.

Participants who still experience clinical benefit at the End of Trial will discontinue from the study and continue treatment per standard of care (SOC). A number of options for ensuring continued supply with lorlatinib will be considered based on the local availability of the treatment and local country laws/regulation.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol. Participant eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before participants are included in the study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be ≥18 years of age inclusive (or ≥ 20 years of age if required by local regulation), at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants must have evidence of histologically or cytologically confirmed diagnosis of metastatic NSCLC (Stage IV, American Joint Committee on Cancer [AJCC] v7.0) that carries an ALK rearrangement, as determined by the Food and Drug Administration (FDA) approved fluorescence in situ hybridization (FISH) assay (Abbott Molecular Inc) or by Immunohistochemistry (IHC) (Ventana Inc).
3. Disease Status Requirements: disease progression after alectinib or ceritinib as first line therapy (the study will limit enrollment of participants with best response of progression or indeterminate on prior alectinib to 8 participants). Participants may have had prior chemotherapy, but only if before starting treatment with alectinib or ceritinib.
4. Tumor Requirements: All Participants must have at least one measurable target extracranial lesion according to RECIST v1.1. Participants with asymptomatic CNS metastases (including participants controlled with stable or decreasing steroid use within the last 2 weeks prior to study entry) will be eligible. The brain metastases may be newly diagnosed or be present as progressive disease after surgery, whole brain radiotherapy or stereotactic radiosurgery. Participants who have leptomeningeal disease (LM) or carcinomatous meningitis (CM) will be eligible if the LM/CM is visualized on magnetic resonance imaging (MRI) or if documented baseline cerebral spinal fluid (CSF) positive cytology is available.
5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
6. Adequate bone marrow functioning, including:
    a. Absolute Neutrophil Count (ANC) $\geq$1,500/mm^3 or $\geq$1.5 x 10^9/L;
    b. Platelets $\geq$100,000/mm^3 or $\geq$100 x 10^9/L;
    c. Hemoglobin $\geq$9 g/dL.
7. Adequate pancreatic function, including:
    a. Serum total amylase $\leq$1.5 x upper limit of normal (ULN)*;
    b. Serum lipase $\leq$1.5 ULN.
    *if total amylase >1.5 x ULN, but pancreatic amylase is within the ULN, the participant may be enrolled.
8. Adequate renal function, including:
    a. Serum creatinine $\leq$1.5 x ULN or estimated creatinine clearance $\geq$60 mL/min as calculated using the method standard for the institution.
9. Adequate liver function, including:
    a. Total serum bilirubin $\leq$1.5 x ULN;
    b. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) $\leq$2.5 x ULN ($\leq$5.0 x ULN in case of liver metastases).
10. Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade $\leq$1 except for adverse events (AEs) that in the investigator' judgment do not constitute a safety risk for the participant.
11. Systemic anti-cancer therapy with alectinib or ceritinib discontinued within a minimum of 5 half-lives prior to first dose of lorlatinib on the study (unless clinically meaningful tumor flare per discretion of the investigator, in which discussion with the sponsor is warranted).

Sex

12. Male or Female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants:

Male participants are eligible to participate if they agree to the following during the intervention period and for at least 98 days after the last dose of study intervention:

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual or homosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent.

  OR
- Must agree to use contraception/barrier as detailed below:
  - Agree to use a male condom when engaging in any activity that allows passage of ejaculate to another person.
  - Female partner of childbearing potential who is currently not pregnant must use an additional highly effective contraceptive method with a failure rate of <1% per year as described in Appendix 4 if having sexual intercourse with male participant.

b. Female participants:

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP) (refer to Appendix 4) for definition.

  OR
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4 during the intervention period and for at least 35 days after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) for the

purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive (at least 25 IU/Ml) pregnancy test (urine or serum as required by local regulations) immediately before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.6.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

13. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
14. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Prior ALK TKI treatment or anti-cancer treatment other than first line alectinib or ceritinib.
2. Spinal cord compression unless the participant has good pain control attained through therapy, and there is stabilization or recovery of neurological function for the 4 weeks prior to randomization.
3. Gastrointestinal abnormalities, including inability to take oral medication; requirement for intravenous alimentation; prior surgical procedures affecting absorption including total gastric resection or lap band; active inflammatory gastrointestinal disease, chronic diarrhea, symptomatic diverticular disease; treatment for active peptic ulcer disease in the past 6 months; malabsorption syndromes.
4. Active and clinically significant bacterial, fungal, or viral infection including hepatitis B virus (HBV) or hepatitis C virus (HCV) (eg, in case of known hepatitis b surface antigen [HBsAg] or HCV antibody positivity), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS) related illness.

5. Clinically significant vascular (both arterial and venous) and non-vascular cardiac conditions, (active or within 3 months prior to enrollment), which may include, but are not limited to:
    a. Arterial disease such as cerebral vascular accident/stroke (including Transient Ischemic Attack [TIA]), myocardial infarction, unstable angina;
    b. Venous diseases such as cerebral venous thrombosis, symptomatic pulmonary embolism;
    c. Non vascular cardiac disease such as congestive heart failure (New York Heart Association Classification Class ≥ II), second degree or third degree atrioventricular (AV) block (unless paced) or any AV block with PR interval >220 msec; or ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 beats per minute (bpm) (unless participant is otherwise healthy such as long distance runners, etc.), machine read Electrocardiogram (ECG) with QTc >470 msec, or congenital long QT syndrome.
6. Participants presenting with abnormal Left Ventricular Ejection Fraction (LVEF) by echocardiogram or Multi-Gated Acquisition Scan (MUGA) according to institutional lower limits.
7. Participants with predisposing characteristics for acute pancreatitis according to investigator judgment (eg, uncontrolled hyperglycemia, hypertriglyceridemia, current gallstone disease, alcoholism [more than 4 drinks on any day or 14 drinks per week where 1 drink is defined as the alcoholic beverage containing approximately 14 grams of pure alcohol, eg, 12 fl oz/360 mL regular beer or 5 fl oz/150 mL of wine] in the last month.
8. History or known presence of interstitial fibrosis, interstitial lung disease, pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, obliterative bronchiolitis, and pulmonary fibrosis.
9. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the participant inappropriate for entry into this study.
10. Evidence of active malignancy (other than current NSCLC, non-melanoma skin cancer, in situ cervical cancer, papillary thyroid cancer, ductal carcinoma in situ (DCIS) of the breast or localized and presumed cured prostate cancer) within the last 3 years prior to randomization.

Prior/Concomitant Therapy

11. Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study entry. Palliative radiation (≤10 fractions) must have been completed at least 48 hours

prior to study entry. Stereotactic or small field brain irradiation must have completed at least 2 weeks prior to study entry. Whole brain radiation must have completed at least 4 weeks prior to study entry.

12. Prior irradiation to >25% of the bone marrow.
13. Concurrent use of any of the following food or drugs (consult the sponsor if in doubt whether a food or a drug falls into any of the above categories) within 12 days prior to the first dose of lorlatinib:

    a. Known strong CYP3A inducers (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort).

    b. Known strong CYP3A inhibitors (eg, strong CYP3A4 inhibitors: grapefruit juice or grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos], boceprevir, cobicistat, clarithromycin, conivaptan, diltiazem, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, paritaprevir and posaconazole, ritonavir, alone and with danoprevir or elvitegravir or indinavir or lopinavir or paritaprevir or ombitasvir or dasabuvir or saquinavir or tipranavir, telaprevir, troleandomycin, and voriconazole, grapefruit juice or grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos]). The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed. Note that strong CYP3A inhibitors can be stopped up to one day prior to first dose of lorlatinib on study.

    c. Known CYP3A substrates with narrow therapeutic index, such as astemizole*, terfenadine*, cisapride*, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, alfentanil, fentanyl (including transdermal patch) or ergot alkaloids (ergotamine, dihydroergotamine) (*withdrawn from United States [US] market).

    d. Known permeability glycoprotein (P-gp) substrates with a narrow therapeutic index (eg, digoxin).

14. Major surgery within 4 weeks prior to enrollment. Minor surgical procedures (eg, port insertion) are not excluded, but sufficient time should have passed for adequate wound healing.

Other Exclusions

15. Known prior or suspected severe hypersensitivity to study interventions or any component in their formulations.
16. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or Pfizer employees, including their family members, directly involved in the conduct of the study.

5.3. Lifestyle Considerations

1. See Appendix 4 for mandatory contraception information.

2. Refrain from consumption of grapefruit/grapefruit related citrus fruits (eg, Seville oranges pomelos) from 1 day before the start of study intervention until after the final dose.

3. Lorlatinib has moderate influence on the ability to drive and use machines. Cautions should be exercised when driving or operating machines as participants may experience CNS effects.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

ARM Name	Lorlatinib 100 mg QD
Intervention Name	lorlatinib
Type	Small molecule
Dosage Form	Tablet
Dose Strength	25 mg
Dosage	100 mg QD
Route of Administration	Oral
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Study Intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	PF-06463922/lorlatinib

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record.
4. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product (IP) manual.
5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.
6. Study interventions should be stored in their original containers and in accordance with the labels.
7. Site staff will instruct participants on the proper storage requirements for take-home study intervention.
8. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer upon discovery. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.
9. The sponsor or designee will provide guidance on the destruction of unused study intervention (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

6.3. Measures to Minimize Bias: Randomization and Blinding

Open-label using IVRS/IWRS	This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an interactive voice response system (IVRS)/interactive web response system (IWRS). The site will contact the IVRS/IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form, if required.

6.4. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned tablets. Deviation(s) from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

6.5. Concomitant Therapy

All concomitant medications and non-drug supportive interventions should be recorded in the CRF until the participant has completed 35 cycles of treatment (approximately 24 months). After cycle 35 the data will be reported in the medical chart, but not collected in the CRF.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Prohibited Concomitant Treatments

Concomitant treatment considered necessary for the participant's wellbeing may be given at discretion of the treating physician.

In vitro studies have demonstrated that CY3A and UGT1A4 are primarily involved in the metabolism of lorlatinib, with additional minor contribution from cytochrome P450 (CYP)2C8, CYP2C19, CYP3A5 and UGT1A3. Inhibition or induction of the above enzymes may result in potential alteration of lorlatinib systemic exposure.

To protect participant safety the following cautions are provided:

- Lorlatinib metabolism may be inhibited by strong CYP3A4/5 inhibitors leading to a potential increase in lorlatinib toxicities. Concomitant administration of lorlatinib with strong CYP3A4/5 inhibitors (e.g. boceprevir, cobicistat, itraconazole,

ketoconazole, posaconazole, troleandomycin, voriconazole, ritonavir, paritaprevir in combination with ritonavir and ombitasvir and/or dasabuvir, and ritonavir in combination with either elvitegravir, indinavir, lopinavir or tipranavir) may increase lorlatinib plasma concentrations. Grapefruit products may also increase lorlatinib plasma concentrations and should be avoided. An alternative concomitant medicinal product with less potential to inhibit CYP3A4/5 should be considered. If a strong CYP3A4/5 inhibitor must be co-administered, the starting lorlatinib dose of 100 mg once daily should be reduced to once daily 75 mg dose. In participants who have had a dose reduction to 75 mg orally once daily due to adverse reactions and who initiate a strong CYP3A4/5 inhibitor, reduce lorlatinib dose to 50 mg orally once daily. If concurrent use of the strong CYP3A4/5 inhibitor is discontinued, lorlatinib should be resumed at the dose used prior to the initiation of the strong CYP3A4/5 inhibitor and after a washout period of 3 to 5 half-lives of the strong CYP3A4/5 inhibitor. The participant should be closely monitored for safety and reduction of the lorlatinib dose if necessary.

- The use of a strong CYP3A4/5 inducer (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort) with lorlatinib is contraindicated and it should be avoided, if possible, as they may also reduce lorlatinib plasma concentration Furthermore, when lorlatinib was coadministered with rifampin (Study B7461011), increases in AST and ALT were noted. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating lorlatinib and until study treatment discontinuation. In addition, use with moderate CYP3A inducers should be avoided due to the potential reduction in lorlatinib exposure.

- Lorlatinib inhibits CYP2C9 (in vitro), so concurrent use of drugs that are CYP2C9 substrates with narrow therapeutic indices, such as warfarin, phenytoin or celecoxib, may have increased effect. Concomitant CYP2C9 substrates should be used with caution, as the net clinical effect of lorlatinib on CYP2C9 is currently being investigated.

- Lorlatinib induces CYP2B6 (in vitro) so concurrent use of drugs that are CYP2B6 substrates, such as bupropion and efavirenz, may have less effect. Concomitant CYP2B6 substrates (e.g. bupropion, efavirenz) should be used with caution, as the net clinical effect of lorlatinib on CYP2B6 is currently being investigated.

- In vitro studies indicated that lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A4/5 and it activates the human pregnane-X-receptor (PXR), with the net effect in vivo being induction. Thus, concurrent administration of lorlatinib with CYP3A4/5 substrates with narrow therapeutic indices, including but not limited to alfentanil, ciclosporin dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus and tacrolimus, should be avoided since the concentration of these medicinal products may be reduced by lorlatinib. However, if it is absolutely necessary to use, sponsor approval is required and the dose of the CYP3A4/5 substrate may need to be increased. The narrow therapeutic index (NTI) CYP3A4/5 substrate should be started only after at least 14 days of

continuous lorlatinib dosing. If there is a change in the lorlatinib dosing regimen such as a dosing interruption or dose reduction, the administration of the NTI CYP3A4/5 substrate should be stopped and resumed at a readjusted dose only after at least 14 days of resumed lorlatinib dosing.

- In vitro studies indicated that lorlatinib may inhibit P-gp (systemically and at the gastrointestinal tract), breast cancer resistance protein (BCRP) (gastrointestinal [GI] tract), OATP1B1, OATP1B3, OCT1, MATE1 and OAT3 at clinically relevant concentrations. The concurrent use of drugs which are P-gp substrates with narrow therapeutic index, such as digoxin is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered. If absolutely necessary to use during the study, it should be initiated following sponsor approval, and be used then with caution. The net clinical effect of lorlatinib on P-gp is currently being investigated.

- In vitro studies indicated that lorlatinib may have the potential to inhibit UGT1A1.

Other Anti-Tumor or Experimental Drugs

No additional systemic anti-tumor therapy will be permitted while participants are receiving a study therapy. Additionally, the concurrent use of select herbal supplements (St John's wort, ginseng, and goldenseal)[15] is not permitted.

Hematopoietic Growth Factors

Primary prophylactic use of granulocyte-colony stimulating factors is not permitted during the first cycle but they may be used to treat treatment emergent neutropenia as per standard of care.

If approved and available for use per country regulations, erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

6.5.2. Permitted Concomitant Treatments

Bisphosphate Therapy

Bisphosphonate therapy for metastatic bone disease is permitted. Bisphosphonate therapy should be given as per local medical practice.

Lipid-Lowering Therapy

Since statins can be metabolized or inhibited by the same CYP450 pathways as lorlatinib (Table 1), pitavastatin or pravastatin followed by rosuvastatin should be the agents to use concomitantly with lorlatinib since they are the least involved with the CYP450 enzyme systems. However, no clinical drug-drug interactions have been formally studied with lorlatinib and careful monitoring is advised.

Table 1. Pharmacokinetic Properties of Statins

	Pitavastatin	Pravastatin	Rosuvastatin	Atorvastatin	Simvastatin	Lovastatin	Fluvastatin
	Livalo	Pravachol	Crestor	Lipitor	Zocor	Mevacor, Altocor	Lescol
Metabolism†	++	+	+	+++	+++	+++	+++
Metabolizing CYP enzymes (of lactone or acid form)	(2C9)	(3A4)	2C9 (2C19)	3A4 (2C8)	3A4 2C8	3A4 2C8	2C9
Inhibitor of CYP3A4‡	-	-	+	+	+	+	+
Inhibitor of CYP2C9‡	-	-	(+)	-	-	-	+
Triglyceride lowering effect	22%-31%**	11%-14%*	17%*	14%-19%*	10%-14%*	13%*	5%***

Adapted from Neuvonen et al, 2006[16].
Parentheses indicate minor significance.
†Three plus signs indicate extensively metabolized, and 1 plus sign indicates limited metabolism, eliminated mainly unchanged.
‡A plus sign indicates yes, and a minus sign indicates no.
* Baseline TG 100-200 mg/dL; Effect of Statins vs Placebo on Triglyceride Levels in 10 Primary and Secondary Placebo-Controlled Outcome Trials table in Miller 2009[17].
** Baseline TG ≥150 mg/dL; Kajinami et al, 2003[18].
*** Schaefer et al, 2004[19].

If hypertriglyceridemia requires treatment beyond a statin that was administered for hypercholesterolemia, fenofibrate or fish oils followed by nicotinic acid should be administered as they have the least involvement with the CYP450 enzyme systems (Table 2). No clinical drug-drug interactions have been formally conducted with lorlatinib and agents listed in Table 2 so careful monitoring is advised.

Table 2. Pharmacokinetic properties of Lipid Lowering Agents

			Fibric Acids	**Fish Oils**
Generic Name	Nicotinic Acid	Gemfibrozil	Fenofibrate	Ethyl esters of omega-3 fatty acids
Tradename	Niaspan®, Nicor®[a]	Lopid®[b]	TriCor®[c]	Lovaza®[d]
Dose	100–2000 mg QD	600 mg BID	200 mg QD	4 gm QD/ 2 gm BID
Metabolism‡	-	-	-	-
Metabolizing CYP enzymes (of lactone or acid form)‡	-	-	-	-
Inhibitor of CYP3A4‡	-	-	-	-
Inhibitor of CYP2C9‡	-	+++	++	-
Inhibitor of CYP2C19‡	-	++	+	-
Inhibitor of CYP1A2‡	-	+	-	-
Triglyceride lowering effect (TG ≥150 mg/dL)	20%-50%*	20%-50%*	36%-55%[e]	45%
Drug Interactions	Caution should be used when prescribing niacin with statins	Concomitant administration with statins is contraindicated	May increase exposure to pravastatin and its metabolite (13%-26%) when used concomitantly	-

‡A plus sign indicates yes, and a minus sign indicates no.
* NCEP-ATP III, 2001.
BID = twice daily; QD = once daily.
a. PI, 4/2015
b. PI, 11/2014
c. PI, 12/2014
d. PI, 05/2014
e. Primary hypertriglyceridemia – severe hypertriglyceridemia (Baseline TG levels 500 to 1500 mg/dL)

Radiotherapy

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions providing the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of lorlatinib with radiotherapy, lorlatinib

treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment after recovery from acute radiation toxicities to baseline.

Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and lorlatinib required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping lorlatinib is recommended at least 2 days prior to surgery. Postoperatively, the decision to reinitiate lorlatinib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6.6. Dose Modification

Dosing interruption or dose reduction may be required based on individual safety and tolerability.

Lorlatinib dose reduction levels are summarized below:

- First dose reduction: 75 mg taken orally once daily
- Second dose reduction: 50 mg taken orally once daily

Lorlatinib should be permanently discontinued if the participant is unable to tolerate the 50 mg dose taken orally once daily.

Dose modification recommendations for toxicities and for participants who develop atrioventricular (AV) block are provided in Table 3

Table 3. Recommended Lorlatinib Dose Modifications for Adverse Reactions

Adverse Reaction[a]	**Lorlatinib Dosing**
Hypercholesterolemia and Hypertriglyceridemia	
Mild hypercholesterolemia (cholesterol between ULN and 300 mg/dL or between ULN and 7.75 mmol/L) **OR** Moderate hypercholesterolemia (cholesterol between 301 and 400 mg/dL or between 7.76 and 10.34 mmol/L) **OR** Mild hypertriglyceridemia (triglycerides between 150 and 300 mg/dL or 1.71 and 3.42 mmol/L) **OR**	Introduce or modify lipid-lowering therapy[b] in accordance with respective prescribing information; continue lorlatinib at same dose.

Table 3. Recommended Lorlatinib Dose Modifications for Adverse Reactions

Adverse Reaction[a]	Lorlatinib Dosing
Moderate hypertriglyceridemia (triglycerides between 301 and 500 mg/dL or 3.43 and 5.7 mmol/L)	
Severe hypercholesterolemia (cholesterol between 401 and 500 mg/dL or between 10.35 and 12.92 mmol/L) **OR** Severe hypertriglyceridemia (triglycerides between 501 and 1,000 mg/dL or 5.71 and 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[b]; if currently on lipid-lowering therapy, increase the dose of this therapy[b] in accordance with respective prescribing information; or change to a new lipid-lowering therapy[b]. Continue lorlatinib at the same dose without interruption.
Life-threatening hypercholesterolemia (cholesterol over 500 mg/dL or over 12.92 mmol/L) **OR** Life-threatening hypertriglyceridemia (triglycerides over 1,000 mg/dL or over 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[b] or increase the dose of this therapy[b] in accordance with respective prescribing information or change to a new lipid-lowering therapy[b]. Withhold lorlatinib until recovery of hypercholesterolemia and/or hypertriglyceridemia to moderate or mild severity grade. Re-challenge at same lorlatinib dose while maximizing lipid-lowering therapy[b] in accordance with respective prescribing information. If severe hypercholesterolemia and/or hypertriglyceridemia recur despite maximal lipid-lowering therapy[b] in accordance with respective prescribing information, reduce lorlatinib by 1 dose level.
Central Nervous System Effects (changes in cognition, mood, or speech)	
Grade 2: Moderate **OR** Grade 3: Severe	Withhold dose until toxicity is less than or equal to Grade 1. Then resume lorlatinib at 1 reduced dose level.
Grade 4: Life-threatening/urgent intervention indicated	Permanently discontinue lorlatinib
Lipase/Amylase Increase	
Grade 3: Severe **OR** Grade 4: Life-threatening/urgent intervention indicated	Withhold lorlatinib until lipase or amylase returns to baseline. Then resume lorlatinib at 1 reduced dose level.
Interstitial Lung Disease (ILD)/Pneumonitis	
Grade 1: Mild **OR** Grade 2: Moderate	Withhold lorlatinib until symptoms have returned to baseline and consider initiating corticosteroids. Resume lorlatinib at 1 reduced dose level. Permanently discontinue lorlatinib if ILD/pneumonitis recurs or fails to recover after 6 weeks of lorlatinib hold and steroid treatment.

Table 3. Recommended Lorlatinib Dose Modifications for Adverse Reactions

Adverse Reaction[a]	Lorlatinib Dosing
Grade 3: Severe **OR** Grade 4: Life-threatening/urgent intervention indicated	Permanently discontinue lorlatinib
PR interval prolongation/Atrioventricular (AV) block	
First Degree AV Block Asymptomatic	Continue lorlatinib at the same dose without interruption. Consider effects of concomitant medicinal products and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely.
First Degree AV Block Symptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If symptoms resolve, resume lorlatinib at 1 reduced dose level.
Second Degree AV Block Asymptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If subsequent ECG does not show second degree AV block, resume lorlatinib at 1 reduced dose level.
Second Degree AV Block Symptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products and assess and correct electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic AV block persists. If symptoms and the second-degree AV block resolve or if participants revert to asymptomatic first-degree AV block, resume lorlatinib at 1 reduced dose level.
Complete AV Block	Withhold lorlatinib. Consider effects of concomitant medicinal products and assess and correct electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Pacemaker placement may be indicated for severe symptoms associated with AV block. If AV block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, resume lorlatinib at full dose. If no pacemaker placed, resume lorlatinib at 1 reduced dose level only when symptoms resolve, and PR interval is less than 200 msec.
Other Adverse Reactions	
Grade 1: Mild **OR**	Consider no dose modification or reduce by 1 dose level, as clinically indicated.

Table 3. Recommended Lorlatinib Dose Modifications for Adverse Reactions

Adverse Reaction[a]	Lorlatinib Dosing
Grade 2: Moderate	
Greater than or equal to Grade 3: Severe	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume lorlatinib at 1 reduced dose level.

Abbreviations: AV=Atrioventricular; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram;
HMG CoA=3-hydroxy-3-methylglutaryl coenzyme A; NCI=National Cancer Institute; ULN=upper limit of normal.

a. Grade categories are based on NCI CTCAE classifications.
b. Lipid lowering therapy may include: HMG CoA reductase inhibitor, nicotinic acid, fibric acid derivatives, or ethyl esters of omega 3 fatty acids.

6.7. Intervention after the End of the Study

At the End of Trial a number of options for ensuring continued supply with lorlatinib will be considered based on the local availability of the treatment and local country laws/regulation.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a patient to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to complete all remaining scheduled assessments.

See Table 3 for dose modification recommendations due to adverse events.

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined Appendix 6 or if the investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula (QTcF) after enrollment (Appendix 7), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed.

See the schedule of activities (SoA) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Note that discontinuation of study intervention does not represent withdrawal from the study.

7.1.1. Temporary Discontinuation

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the Investigator.

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the participant missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in Table 3 unless expressly agreed otherwise following discussion between the Investigator and the Sponsor. If a dose reduction is applied in the same cycle, the participant will need to return to the clinic to receive new drug supply.

In the event of a treatment interruption for reasons other than treatment related toxicity (eg, elective surgery) lasting >1 week, treatment resumption will be decided in consultation with the Sponsor.

Participants not recovering from lorlatinib related toxicity within 42 days since last dose should discontinue lorlatinib treatment.

If a treatment interruption continues beyond Day 21 of the current cycle, then the day when treatment is restarted will be counted as Day 1 of the next cycle. Every effort should be made to maintain the tumor assessments scheduling as every 6 weeks (±1 week) or per local practice versus the date of Cycle 1 Day 1.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

- The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal. The participant will be permanently discontinued both from the study intervention and from the study at that time.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and notify the sponsor accordingly.

- If the participant withdraws from the study and also withdraws consent (see below) 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.

- When a participant withdraws from the study because of an SAE, the SAE must be recorded on the case report form (CRF) and reported on the clinical trial serious adverse event (CT SAE) Report.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

Reasons for withdrawal of study treatment may include:

- Objective disease progression;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Reasons for withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by sponsor;
- Lost to follow-up;
- Refused further follow-up;
- Death.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICF before performing any study-specific procedures.

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

8.1. Efficacy Assessments

8.1.1. Tumor Assessments

Tumor assessments will include all known or suspected disease sites. Computed tomography (CT) or MRI scans of Chest Abdomen Pelvis (CAP) and MRI of the brain will be performed at screening. Gadolinium contrast enhanced MRI must be used for assessment of CNS lesions with contingent slices of 1 mm for lesions 5 mm – 10 mm in size, 5 mm for lesions greater than 10 mm. Bone scans (or bone MRI if preferred by investigator) will be performed at baseline for all participants and repeated every 12 weeks on study only if evidence of bone metastases is observed at baseline (however, if a participant has bone involvement, assessment of those sites via appropriate modality is required every 6 weeks ±1 week up to 24 months or progressive disease whichever occurred first). For all tumor assessments, the method of assessment that was used at baseline should be the same method used throughout the study. CT and MRI scans to be done at every 6 weeks ±1 week up to approximately 24 months (cycle 35) and then as per local clinical practice. Tumor assessment should be repeated at the end of treatment if more than 6 weeks have passed since the last evaluation. Tumor assessment should not be repeated at the end of treatment if progression occurs when the participant has shifted to the local clinical practice. Moreover, radiological tumor assessments will be conducted whenever disease progression is suspected (eg, symptomatic deterioration).

Assessment of response will be made using RECIST version 1.1 (Appendix 5). Confirmation of response will be required at least 4 weeks after initial response is observed.

All participants' files and radiologic images must be available for source verification and for peer/independent central radiology review as determined by the sponsor. Instructions for submission of these images will be provided in the Study Reference Manual.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA and in the lorlatinib product information. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems and ECOG status. Weight will also be measured and recorded.

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Electrocardiograms

- Triplicate 12-lead (with a 10-second rhythm strip). ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary. Refer to Section 6.6 for PR interval prolongation/AV block.

- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

- If at any of these time points the mean PR interval is prolonged (≥200 msec) or QTc is prolonged (≥501 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation.

- PR interval prolongation and AV block have been reported in participants receiving lorlatinib. ECG will be monitored prior to initiating lorlatinib and monthly thereafter, particularly in participants with predisposing conditions to the occurrence of clinically significant cardiac events. Dose modification may be required for those participants who develop AV block (See Section 6.6).

- ECG values of potential concern are listed in Appendix 7.

8.2.3. Echocardiograms/Multigated (MUGA) Acquisition Scan

Echocardiogram or MUGA will be performed at screening. Additional assessments may be performed as clinically indicated and according to lorlatinib product information. LVEF decrease has been reported in participants receiving lorlatinib. In participants who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring, including LVEF assessment, should be considered. The same method should be used throughout the study.

For France and Germany, a transthoracic echocardiogram (TTE) will be performed every 6 months (± 2 weeks) during treatment, and only at the end of treatment visit if the previous assessment was > 1 month. Pulmonary arterial pressure (PAP) will be assessed.

8.2.4. ECOG Performance Status

Refer to Appendix 9 for ECOG Performance Status Criteria.

8.2.5. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The use of lorlatinib has been associated with increases in serum cholesterol and triglycerides. Serum cholesterol and triglycerides should be monitored before initiation of lorlatinib; 2, 4 and 8 weeks after initiating lorlatinib; and regularly

thereafter. Initiate or increase the dose of lipid-lowering medicinal products, if indicated (see Section 6.6).

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator, then the SAE or AE or dose modification must be recorded in the CRF.

8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in women of childbearing potential (WOCBP) at the times listed in the SoA (Section 1.3). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected), at the end of the study, and at follow-up. Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.
AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE, or that caused the participant to discontinue the study intervention (see Section 7).

In addition, the investigator may be requested by Pfizer Safety to obtain the adequate supporting documentation, including laboratory tests and cardiac assessments, to elaborate the AEs and SAEs occurring during the course of the study and any subsequent safety follow-up. in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the last administration of the investigational product.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period are reported to Pfizer Safety on the clinical trial SAE Report Form immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment.

SAEs occurring in a participant after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

8.3.1.2. Recording Non-serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

If a participant begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the 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 participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SmPC and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 35 and 98 days for female and male participants, respectively after the last dose.

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Medication Errors

Medication errors may result from the administration or consumption of the investigational product by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, are recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

8.4. Treatment of Overdose

For this study, any dose of lorlatinib greater than 100 mg within a 24-hour time period will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose. There is no antidote for lorlatinib.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and given the dose dependent effect on PR interval, ECG monitoring is recommended.

3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with a SAE**.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic samples are not being collected in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

8.7.1. Specified Genetics

Genetics (specified analyses) are not evaluated in this study.

8.7.2. Banked Biospecimens for Genetics

Banked biospecimen samples are not being collected in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Health Economics

Not applicable to this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

The primary objective of the study is to evaluate overall and intracranial anti-tumor activity of single-agent lorlatinib in participants with advanced ALK-positive NSCLC whose disease has progressed on alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy, by showing a superiority of lorlatinib versus historical control, of which the ORR is ≤30%. The study will be considered to show this superiority if the lower limit of the 95% confidence interval around the estimated ORR excludes 30%.

Tumor responses and progressions will be evaluated as per RECIST V 1.1.

9.1.1. Estimands

The primary estimand by ICR is the treatment effect of lorlatinib from time of first dose until progression is met or subsequent anti-cancer therapy is administered for all participants who receive at least one dose of lorlatinib without regard to discontinuation from treatment.

Point estimates of ORR (defined as the percentage of participants with confirmed complete response [CR] or confirmed partial response [PR]) and confidence intervals (following the methodology outlined in Section 9.4.1) will be calculated. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

The definition of primary estimand also applies to the secondary endpoint of OR by INV, except that the treatment effect is based on INV.

The estimand for intracranial objective response (IC-OR) by ICR/INV is the intra cranial treatment effect of lorlatinib from time of first dose until intra cranial progression is met or subsequent anti-cancer therapy is administered for all participants who receive at least one dose of lorlatinib without regard to discontinuation from treatment.

Point estimates of intracranial objective response rate (IC-ORR) by ICR/INV (defined as the percentage of participants with confirmed CR or confirmed PR in brain) and confidence intervals (following the methodology outlined in Section 9.4.1) will be calculated. Both CR and PR in brain must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

The estimand for TTR by ICR/INV is the treatment effect from the time of first dose to the first date of OR (CR or PR) that is subsequently confirmed for responders to lorlatinib. TTR is defined as the time from the date of first dose to the date of first documentation of confirmed OR (CR or PR).

The estimand for DOR by ICR/INV is the treatment effect from the first date of OR that is subsequently confirmed for responders to lorlatinib until progression or death, without regard to discontinuation from treatment unless new anti-cancer therapy is initiated or extended gap in tumor assessment is present prior to progression or death. DOR is defined as the time from first documentation of confirmed OR (CR or PR) to the date of first documentation of progression of disease (PD) or death due to any cause, whichever occurs first.

The estimand for IC-DOR by ICR/INV is the treatment effect from the first date of OR that is subsequently confirmed in brain for responders to lorlatinib, until intra cranial progression or death, without regard to discontinuation from treatment unless new anti-cancer therapy is initiated or extended gap in tumor assessment is present prior to intra cranial progression or death. IC-DOR is defined as the time from first documentation of confirmed OR in brain (CR or PR) to the date of first documentation of PD in brain or death due to any cause, whichever occurs first.

The estimand for TTP by ICR/INV is the treatment effect from the time of first dose for all participants who receive at least one dose of lorlatinib until progression, without regard to

discontinuation from treatment unless death occurs, new anticancer therapy is initiated or an extended gap in tumor assessment is present prior to progression. TTP is defined as the time from date of first dose to the date of the first documented PD due to any cause.

The estimand for PFS by ICR/INV is the treatment effect from the time of first dose for all participants who receive at least one dose of lorlatinib until progression or death due to any cause, without regard to discontinuation from treatment unless new anticancer therapy is initiated or an extended gap in tumor assessment is present prior to progression or death. PFS is defined as the time from date of first dose to the date of the first documented disease progression or death due to any cause, whichever occurs first.

9.2. Sample Size Determination

The primary endpoint is Objective tumor response assessed by RECIST version 1.1 per ICR. Analysis of tumor response will be based on both Overall tumor response and on Intra-Cranial tumor response.

OR is defined as a confirmed CR or confirmed PR from the first dose of study treatment until disease progression, start of anticancer therapy or death due to any cause. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.

ORR is defined as the proportion of treated participants with confirmed CR or confirmed PR per ICR assessment and will be estimated together with its 2-sided exact 95% CI (using an exact Clopper-Pearson CI).

According to literature, platinum-based doublet chemotherapy in patients with ALK + NSCLC refractory to second generation TKIs has an objective response rate of approximately 30%.[20] Setting as target for lorlatinib a response rate of about 43% (as observed in cohort EXP-3B of phase 2 portion of study B7461001), a sample size of 60 participants would result in an exact two-sided 95% CI of the ORR with lower limit of the CI greater than 30%. In order to compensate for a potential 15% drop out rate (participants with death prior to first post-baseline assessment, inadequate baseline assessment, new anti-cancer therapy started prior to first post-baseline assessment, post-baseline disease assessments missing), the overall sample size for the study is set to 70 participants.

The study will be considered to have met its primary endpoint if the lower limit of the 95% confidence interval around the estimated ORR excludes 30%.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Intent to Treat (ITT)/Safety	All enrolled participants who take at least 1 dose of lorlatinib

Population	Description
Per Protocol Population: Participants with CNS metastases based on Independent Central Review	Subset of the ITT analysis set including only participants with CNS metastases at study entry (i.e. with Lesions having Disease Site=Brain) according to Independent Central Review
Per Protocol Population: Participants with CNS metastases based on Investigator Assessment	Subset of the ITT analysis set including only participants with CNS metastases at study entry (i.e. with Lesions having Disease Site=Brain) according to Investigator Assessment

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	**Confirmed OR by ICR** • Population: ITT Using an exact method based on binomial distributions, estimate the confirmed ORR by ICR and corresponding two-sided 95% CI, based on OR from the time of first dose until progression is met or subsequent anti-cancer therapy is administered without regard to discontinuation from treatment. Participants with death prior to first post-baseline assessment, inadequate baseline assessment, new anti-cancer therapy started prior to first post-baseline assessment, and all post-baseline disease assessments missing will be considered as non-responders.
Secondary	**Confirmed OR by INV** • Population: ITT Use the same statistical analysis methods as for the primary endpoint except that the treatment effect is based on INV. **Confirmed IC-OR by ICR** • Population: Per protocol population of participants with CNS metastases based on Independent Central Review

Endpoint	Statistical Analysis Methods
	Using an exact method based on binomial distributions, estimate the confirmed IC-ORR by ICR and corresponding two-sided 95% CI, based on intra cranial OR from the time of first dose until intra cranial progression is met or subsequent anti-cancer therapy is administered without regard to discontinuation from treatment. Participants with death prior to first post-baseline assessment, inadequate baseline assessment, new anti-cancer therapy started prior to first post-baseline assessment, and all post-baseline disease assessments missing will be considered as non-responders. **TTR by ICR/INV and IC-TTR by ICR/INV** • TTR is defined as the time from first dose to first documentation of objective tumor response (CR or PR) that is subsequently confirmed. For patients whose OR proceeds from PR to CR, the onset of PR is taken as the onset of response. TTR will only be calculated for the subgroup of patients with a confirmed objective tumor response. All the analyses will be repeated also for Time to Intracranial Response (IC-TTR) considering patients with intracranial response (i.e. Best Overall Intracranial Response as confirmed Complete Response (CR) or confirmed Partial Response (PR) considering only the Lesions having Disease Site=Brain). TTR and IC-TTR will be summarized based on both ICR and derived investigator assessments using descriptive statistics. **DOR by ICR/INV** • Using the Kaplan-Meier method, estimate its associated statistics on DOR (including the median DOR with two-sided 95% CI) for responders to lorlatinib, without regard to discontinuation from treatment unless new anti-cancer therapy is initiated or extended gap in tumor assessment is present prior to progression or death. DOR is defined as the time from first documentation of OR (CR or PR) that is subsequently confirmed to the date of first documentation of PD or death due to any cause, whichever occurs first. This analysis is based on responders only from the ITT population. Participants with an event more than 12 weeks (24 weeks post the first 42 weeks) after the last adequate tumor assessment will be censored on the date of the last adequate tumor assessment prior to the gap that documented no progression. If a new anti-cancer therapy starts prior to an event, the participant will be censored on the date of the last adequate tum or assessment that documented no

Endpoint	Statistical Analysis Methods
	progression prior to start of the new anti-cancer therapy. The CI for the median DOR will be calculated according to Brookmeyer and Crowley method. **IC-DOR by ICR/INV** • Using the Kaplan-Meier method, estimate its associated statistics on IC-DOR (including the median IC-DOR with two-sided 95% CI) for intra cranial responders to lorlatinib, without regard to discontinuation from treatment unless new anti-cancer therapy is initiated or extended gap in IC tumor assessment is present prior to progression or death. IC-DOR is defined as the time from first documentation of IC-OR (CR or PR) that is subsequently confirmed to the date of first documentation of intra cranial PD or death due to any cause, whichever occurs first. This analysis is based on intra cranial responders only from Participants with CNS metastases populations. Participants with an event more than 12 weeks (24 weeks post the first 42 weeks) after the last adequate tumor assessment will be censored on the date of the last adequate tumor assessment prior to the gap that documented no progression. If a new anti-cancer therapy starts prior to an event, the participant will be censored on the date of the last adequate tumor assessment that documented no progression prior to start of the new anti-cancer therapy. The CI for the median DOR will be calculated according to Brookmeyer and Crowley method. **TTP by ICR/INV** • Using the Kaplan-Meier method, estimate its associated statistics on TTP (including the median TTP with two-sided 95% CI, the TTP rates at clinically meaningful timepoints with two-sided 95% CI) for all participants who received at least one dose of lorlatinib without regard to discontinuation from treatment unless death occurs, new anti-cancer therapy is initiated or extended gap in tumor assessment is present prior to progression. TTP is defined as the time from date of first dose to the date of the first documented PD. This analysis is based on ITT population. Participants with an event more than 12 weeks (24 weeks post the first 42 weeks) after the last adequate tumor assessment will be censored on the date of the last adequate tumor assessment prior to the gap that documented no progression. If the participant dies before progression, the participant will be censored on the date of death. If a new anti-cancer therapy starts prior to an event, the participant will be censored on the date of the last adequate tumor assessment that

Endpoint	Statistical Analysis Methods
	documented no progression prior to start of the new anti-cancer therapy. Participants with inadequate baseline assessment or with no adequate post-baseline tumor assessments within 12 weeks after the start date will be censored on the start date, unless the participant dies within 12 weeks of the start date, in which case, the patient will be censored on date of death. The CI for the median TTP will be calculated according to Brookmeyer and Crowley method, and the CIs for the survival function estimates at the timepoints will be derived using the log(-log) method. **PFS by ICR/INV** • Using the Kaplan-Meier method, estimate its associated statistics on PFS (including the median PFS with two-sided 95% CI, the PFS rates at clinically meaningful timepoints with two-sided 95% CI) for all participants who received at least one dose of lorlatinib without regard to discontinuation from treatment unless new anti-cancer therapy is initiated or an extended gap in tumor assessment is present prior to progression or death. PFS is defined as the time from date of first dose to the date of the first documented PD or death due to any cause, whichever occurs first. This analysis is based on ITT population. Participants with an event more than 12 weeks (24 weeks post the first 42 weeks) after the last adequate tumor assessment will be censored on the date of the last adequate tumor assessment prior to the gap that documented no progression. If a new anti-cancer therapy starts prior to an event, the participant will be censored on the date of the last adequate tumor assessment that documented no progression prior to start of the new anti-cancer therapy. Participants with inadequate baseline assessment or with no adequate post-baseline tumor assessments within 12 weeks after the start date will be censored on the start date, unless the participant dies within 12 weeks of the start date, in which case, death will be an event on date of death. The CI for the median PFS will be calculated according to Brookmeyer and Crowley method, and the CIs for the survival function estimates at the timepoints will be derived using the log(-log) method.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Drug exposure will be summarized using descriptive statistics.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The investigator will classify the severity of AEs using the CTCAE v4.03. A treatment emergent AE (TEAE) is defined as any event that occurs for the first time during the on-treatment period or AEs that were observed prior to the start of study treatment but increased in severity during the on-treatment period. Only TEAEs with an onset date prior to date of last dose + 28 days or the date of initiation of a new anti-cancer therapy (whichever occurs first) will be tabulated in summary tables. All data will be listed.
The number and percentage of participants with AEs will be summarized by MedDRA system organ class, preferred term, relationship to study intervention, and severity. A by-participant listing will be provided for those participants who experience an SAE, including death, or experience an AE associated with discontinuation of study intervention.

9.5. Interim Analyses

No interim analysis is planned for this study.

9.5.1. Data Monitoring Committee (DMC)

This study will not use a data monitoring committee.

9.5.2. Independent Central Radiological Review

An independent core imaging laboratory will be used in this study. All sites will be required to submit images to the core imaging laboratory for ICR as soon as they are performed at the site so that imaging scans may be read in real time. The requirements of submitting images will be provided to sites by the core imaging laboratory.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICF, SmPC, and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational 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 participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The investigator must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data related to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The investigator further must ensure that each study participant 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.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

10.1.4. Data Protection

- All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

- Participants' 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, participants will be assigned a single, participant-specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

10.1.5. Committees Structure

See Section 9.5.2.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its standard operating procedures (SOPs).

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. US Basic Results are generally submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts public disclosure synopses (Clinical Study Report [CSR] synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contribute to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The

investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

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

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the clinical monitoring plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for so long as they are maintained.

- When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

- The investigator(s) will notify sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with sponsor or its agents to prepare the investigator site for the inspection and will allow sponsor or its agent, whenever feasible, to be present during the

inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

- Definition of what constitutes source data can be found in the clinical monitoring plan.

10.1.9. Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to contract research organization (CRO) if requested to do so by the responsible IRB/IEC or if such termination is required to protect the health of Study Participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator

- Discontinuation of further study intervention development

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol the contract will control as to termination rights.

10.1.10. Publication Policy

- The results of this study may be published or presented at scientific meetings by the Investigator after publication of the overall study results or one year after end of the study (or study termination), whichever comes first.

- The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submit all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary to the appropriate scientific presentation or understanding of the study results.

- For all publications relating to the study, the Investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

- The sponsor will comply with the requirements for publication of the overall study results covering all Investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

- If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.11. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the team SharePoint site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, participant study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. For sites other than

a Pfizer clinical research unit (CRU), the contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for screening pregnancy criteria.
  - For details of timing of recommended pregnancy testing see Section 8.2.6

Table 4. Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Hemoglobin	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Clinical Chemistry[1]	Blood urea nitrogen (BUN) or Urea	Potassium	Aspartate Aminotransferase (AST)	Total bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)	Phosphorus or Phosphate
	Glucose (fasting)	Total Calcium	Alk Phos	Serum total amylase[2]
	Uric Acid	Magnesium	Albumin	Serum lipase
Other Screening Tests	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) • Lipids: Total Cholesterol, low density lipoproteins (LDL), high density lipoproteins (HDL), Triglycerides. The results of each test must be entered into the CRF at screening only or C1D1 if baseline assessment not performed within 7 days before.			

NOTES:
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1 and Appendix 6. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international

Table 4. Protocol Required Safety Laboratory Assessments

normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Pancreatic isoenzyme required if serum total amylase not within normal limits per local institutional ranges.

Investigators must document their review of each laboratory safety report.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

- Examples of such events include invasive or malignant cancers, 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.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with Common Terminology Criteria for Adverse Events (CTCAE) Grade 5 (see the Severity Assessment section).

10.3.3. Recording/Reporting and Follow-Up of AE and/or SAE

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	**None**	All (And exposure during pregnancy [EDP] supplemental form for EDP)

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of CT SAE Report Form /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as “related to investigational product” for reporting purposes, as defined by the sponsor" and "In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

- Contacts for SAE reporting can be found in the investigator site file.

SAE Reporting to Pfizer Safety via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to Pfizer Safety.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the investigator site file.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above conditions can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female
   - A postmenopausal state is defined as age 60 or older or no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Contraception – for women

Female participants must use highly effective contraception while taking study intervention and for at least 35 days after stopping study intervention.

Lorlatinib may reduce the effectiveness of hormonal contraceptive methods; therefore, hormonal contraceptives may not be considered highly effective. If hormonal contraception is unavoidable it must be used in combination with a condom.

Highly Effective Methods That Have Low User Dependency

1. Intrauterine device (IUD).
2. Bilateral tubal occlusion.
3. Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Contraception – for men

Male participants must use a condom while taking study intervention and for at least 98 days after stopping study intervention.

Collection of Pregnancy Information:

For both unapproved/unlicensed products and for marketed products, an EDP occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the study intervention; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the study intervention;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the study intervention prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a participant or participant's partner becomes or is found to be pregnant during the participant's treatment with the study intervention, the investigator must report this

information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. 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 (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

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

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

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

10.5. Appendix 5: RECIST (version 1.1) Tumor Assessment Criteria[21]

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below:

Measurable Lesions

Lesions that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm for lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm for lesions assessed by chest X-ray.
- 15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Non-measurable Lesions

Non-measurable lesions include small lesions (longest diameter <10 mm or pathological lymph nodes with a ≥ 10 but < 15 mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical exam and not measurable by reproducible imaging techniques.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Special Considerations Regarding Specific Lesions

Bone lesions:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Solitary lesions:

If a measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as target lesions and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter of all target lesions will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment.

One exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of ≥ 15 mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

- **Complete Response (CR):** disappearance of all target lesions.
- **Partial Response (PR):** at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression.
- **Stable Disease (SD):** neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the CRF.

Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Response in non-target lesions is defined as follows:

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Cytology, histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

For patients having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the CRF.

New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow-up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

The use of fluorodeoxyglucose (FDG)-PET is sometimes reasonable to complement a CT scan assessment of a PD (particularly for possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up
- No FDG-PET at baseline and a positive FDG-PET at follow- up: if the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Confirmation of Tumor Response

Confirmation of response is required for non-randomized trials with primary endpoint of response, but is not required in randomized studies since the control arm serves as appropriate means of interpretation of data.

Determination of Overall Response by RECIST v 1.1

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 5.

Table 5. Response Evaluation Criteria in Solid Tumors

Target lesions	Non-target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease,
PD = progressive disease, and NE = inevaluable.

Best overall response

The best overall response is determined once all the data for the patient is known. Best response in trials in which confirmation of complete or partial response is not required (ie. randomized trials) is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered non-evaluable.

When confirmation of CR and PR is required (ie, non-randomized trials with primary endpoint of response), the best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an

objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Participants who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For participants with baseline AST OR ALT OR TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy’s law case should be reviewed with the sponsor.The participant should return to the investigator site and be evaluated as soon as possible, preferably within

48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's Law, additional laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time (PT)/international normalized ratio (INR), total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum sample for acetaminophen drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the liver function test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as Adverse Events (AEs)
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >220 msec. • New prolongation of QTcF to >470 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent premature ventricular complexes (PVCs), triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as Serious Adverse Events (SAEs)

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de pointes).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Country-specific Requirements

France specific requirements

1. GCP Training

Prior to enrollment of any subjects, the investigator and any sub-investigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will complete the Pfizer GCP Training or equivalent before performing study-related duties. For studies of applicable duration, the investigator and sub-investigators will complete Pfizer GCP Training or equivalent every three years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Investigational Product

No subjects or third-party payers will be charged for study intervention.

3. Inspections

The investigator(s) will notify Pfizer or its service provider immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its service provider to prepare the study site for the inspection and will allow Pfizer or its service provider (if not prohibited by law) to be present during the inspection. The study site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its service provider. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its service provider with an opportunity to review and comment on responses to any such findings.

10.9. Appendix 9: ECOG Classification of Performance Status

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

10.10. Appendix 10: Abbreviations

Abbreviation	Term
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophils count
AST	aspartate aminotransferase
AV	atrioventicular
BCRP	breast cancer resistance protein
bpm	beats per minute
BID	twice daily
BUN	blood urea nitrogen
CAP	chest abdomen pelvis
C1D1	cycle 1 day 1
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CFR	code of federal regulations
CK	creatine kinase
CM	carcinomatous meningitis
CMA	conditional marketing authorization
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	case report form
CRM	continual reassessment method
CRO	contract research organization
CRU	clinical research unit
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CT SAE	clinical trial serious adverse event
CYP	cytochrome P450
DCIS	ductal carcinoma in situ
DDI	drug-drug interaction
DILI	drug-induced liver injury
DMC	data monitoring committee

Abbreviation	Term
DOR	duration of response
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EML4	echinoderm microtubule-associated protein-like 4
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL	high density lipoprotein
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme
HRT	hormone replacement therapy
IB	investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IC	intracranial
IC-OR	intracranial objective response
IC-ORR	intracranial objective response rate
IC-TTR	time to intracranial response
ICR	independent central review
ID	identification
IHC	immunohistochemistry
ILD	interstitial lung disease
IND	investigational new drug application
INR	international normalized ratio
INV	investigator

Abbreviation	Term
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
ITT	intent to treat
IVR	interactive voice response system
IWR	interactive web response system
KRAS	Kirsten Rat Sarcoma
LDL	low density protein
LFT	liver function test
LPFV	last patient first visit
LM	leptomeningeal meningitis
LVEF	left ventricular ejection fraction
MEDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multigated acquisition
NCI	National Cancer Institute
NE	inevaluable
NSCLC	non-small cell lung cancer
NTI	narrow therapeutic index
OR	objective response
ORR	objective response rate
OS	overall survival
PAES	post authorization efficacy study
PAP	pulmonary arterial pressure
PD	progression of disease
PCD	primary completion date
PET	positron emission tomography
PFS	progression-free survival
P-gp	permeability glycoprotein
PI	principal investigator
PR	partial response
PS	performance status
PT	prothrombin time
PVC	premature ventricular complexes
PXR	human pregnane-X-receptor
QD	once daily
QTcF	Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumor
ROS1	c-ROS oncogene-1
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SmPC	summary of product characteristics
SoA	schedule of activities

Abbreviation	Term
SOC	standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reactions
TBili	total bilirubin
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
TPS	tumor proportion score
TTE	trans thoracic echocardiogram
TTP	time to tumor progression
TTR	time to tumor response
ULN	upper limit of normal
US	United States
WBC	white blood cell
WOCBP	women of childbearing potential

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