CLINICAL PROTOCOL

A PHASE 3, RANDOMIZED, OPEN-LABEL STUDY OF LORLATINIB (PF-06463922) MONOTHERAPY VERSUS CRIZOTINIB MONOTHERAPY IN THE FIRST-LINE TREATMENT OF PATIENTS WITH ADVANCED ALK-POSITIVE NON-SMALL CELL LUNG CANCER

Investigational Product Number:	PF-06463922
Investigational Product Name:	Lorlatinib
United States (US) Investigational New Drug (IND) Number:	CCI [redacted]
European Clinical Trials Database (EudraCT) Number:	2016-003315-35
Protocol Number:	B7461006
Phase:	3

Document History

Document	Version Date	Summary of Changes and Rationale
Original Protocol	05 October 2016	Not Applicable
Amendment 1	21 February 2017	• Schedule of Activities updated for consistency with relevant protocol sections. • Instructions added in Table 4. PR Interval Prolongation Management that in case of complete heart block not followed by pacemaker placement, lorlatinib is permanently discontinued. • Ophthalmology examination updated to be consistent with data collection in the crizotinib studies. • Pharmacogenomics Section 7.13. removed to avoid duplicate sample collection. • DATA ANALYSIS/STATISTICAL METHODS Section 9. amended to specify how homogeneity of treatment effect across centers will be investigated.
Amendment 2	16 April 2018	• Schedule of Activities (SoA) modified to allow use of available results for assessments performed prior to the Informed Consent being obtained. • Pre screening activities to determine ALK status included in SoA and related protocol sections. • SoA updated for consistency with relevant protocol sections. • Time window added for Laboratory exams in SoA: Explanatory notes for Triplicate ECG reported in SoA.

Document	Version Date	Summary of Changes and Rationale
		• Time window added for ECHO and Muga at Screening and further assessment. • Trans Thoracic Echocardiogram to assess Pulmonary Arterial Pressure and right heart functionality added in SoA and paragraph 7.4.6 upon demand of France and Germany Health Authorities. • Clarification provided in SoA and § 7.1 for patients continuing treatment beyond disease. • SoA and related § 6.1 updated to confirm suitability of cytological sampling and Endobronchial Ultrasound Transbronchial biopsies. • The Footnotes # 23 and # 24 in the SoA for Beck Depression Inventory II Scale and the Columbia Suicide Severity Rating Scale updated. • 1.2.5.3 Clinical Data section updated providing the most recent enrollment status for the pivotal study B7461001. • 1.2.8 Summary of Benefit/Risk Assessment section revised with regards to the updated list of lorlatinib identified risks. • Inclusion Criteria #1 reworded for the sake of clarity. • Inclusion Criteria #2 reworded in alignment with the Inclusion Criteria #1. • Exclusion Criteria # 7 revised to be exclusionary of vascular (both arterial and venous) and non-vascular conditions.

Document	Version Date	Summary of Changes and Rationale
		• Exclusion Criteria # 10 revised to allow in situ malignancies which do not currently require treatment. • Exclusion Criteria #11 updated for the CYP 3A inhibitors//inducers list per new FDA classification. • Exclusion Criteria #16 revised based on the updated safety contraception language. Section 4.3.1 Contraception updated accordingly. • Sunlight exposure warning removed, based on phototoxicity results in rats. • Stratification Factors at § 5.1.1 clarified for allocation to Asian or Non Asian stratum. • Additional information/guidance provided in §5.4.3 and §7.2 in case patient continues to be treated with study drug after Progression of Disease and for drug provison after the study ends. • A revised list of suitable statins provided (§5.5.1.1) to support Investigator in the management of elevated lipid levels. • Guidance provided in §5.5.2.6 for data collection in case of Severe Visual Loss. • Section 5.9.1.1 Inhibitors and Inducers of CYP Enzymes updated according to new FDA classification. • Minor updates in section 9. • Updates to Appendix 4.

Document	Version Date	Summary of Changes and Rationale
		• Appendix 7 specific for France included.
Amendment 3	16 January 2019	• Section 4.3 Lifestyle Requirements. This section was updated as per lifestyle guidance reported in the new protocol template and as per contraception requirements of updated product labels. Exclusion criteria 15 (it was #16 in the PA2) was updated accordingly. • Section 5.4.3 Treatment duration. Text was modified to clarify that patients, continuing the treatment beyond confirmed progression by BICR, should undergo the same assessments foreseen during the active treatment period. As far as tumor assessments, if only extracranial progression was documented, with intracranial lesions stable or in response, intracranial assessments should be performed until intracranial PD; once intracranial PD is documented no further tumor assessments are required. • Section 5.9 Concomitant Treatments. Text was updated to align the wording with lorlatinib core data sheet and IB. Exclusion Criteria 11 and 12, were updated accordingly. • Section 7.2 Expedited Blinded Independent Central Review for Disease Progression. Text was modified to clarify that for investigator-assessed disease progression every effort should be made to keep the patient on study treatment and have all the assessments performed as per SoA until the BICR has completed the radiographic image review and confirmed progression. [redacted]

Document	Version Date	Summary of Changes and Rationale
		CCI [redacted] • Schedule of Activities, footnote 31. Text was modified to clarify that the Post Treatment Follow Up visit will continue until PD or until the time of initiation of new anticancer treatment, with the exception of patients continuing to experience treatment related toxicities that 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. CCI [redacted]
Amendment 4	4 October 2019	The group-sequential design of the study based on the primary PFS endpoint as assessed by BICR has been modified by replacing the planned futility analysis, that was to be conducted at 60% information fraction (IF), with an interim efficacy analysis to be conducted at 75% IF. • As a result, Section 9.1 Sample Size Determination and Section 9.6 Interim Analysis, have been revised by replacing the Lan-DeMets (O'Brien-Fleming) spending function to determine the non-binding futility boundary at the interim analysis of PFS with the Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries at

Document	Version Date	Summary of Changes and Rationale
		the interim and final analysis of PFS. CCI [redacted] • Section 9.3.2.7 Clinical Benefit Response has been removed and CBR has been eliminated from the list of secondary endpoints since the protocol already includes more relevant efficacy endpoints. • The actual patient enrollment has also been provided in Section 3 STUDY DESIGN as enrollment has been closed. • Section 2. and 9.3: IC-DR and IC-TTR added. • Section 4.1 Inclusion Criteria, clarification added on the Lung Cancer Staging System. • Section 4.2 Exclusion Criteria and 4.3 Contraception: female contraception period after the last lorlatinib dose extended from 21 to 35 days to align with the Lorviqua SmPC (CHMP Opinion on 28 February 2019 and Commission Decision 06 May 2019). • Section 7.2 Expedited Blinded Independent Central Review for Disease Progression. The process has been clarified. • Schedule of Activities, the collection of subsequent anticancer treatment has been clarified.

Document	Version Date	Summary of Changes and Rationale
		• Typos fixed.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs)/ethics committees (ECs).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

APPENDICES

PROTOCOL SUMMARY

Background and Rationale

Non-small cell lung cancer (NSCLC) is the most common cause of fatal malignancy globally, most often diagnosed in advanced stages, where surgery and local radiotherapy are no longer curative or indicated.[1,2] Standard therapy in advanced stages of disease is primarily palliative in nature, involving the use of cytotoxic chemotherapy with or without radiation therapy or immunotherapy.[3,4,5] Targeted therapies such as tyrosine kinase inhibitors (TKIs) may be used for appropriate patients. In spite of these treatments, 5-year survival is only about 17% for advanced-stage NSCLC patients, highlighting the need for novel therapies and treatment regimens.[6,7]

Molecularly targeted therapy has been successful in NSCLC patients who have tumors that harbor various alterations, including the fusion protein EML4-ALK. The first approved agent for anaplastic lymphoma kinase (ALK)-positive NSCLC was crizotinib. Although most patients with ALK-positive NSCLC derive substantial clinical benefit from crizotinib, some ALK-positive NSCLC patients will not derive any benefit (intrinsic resistance), while other patients who initially derive benefit will develop resistance (acquired resistance). In the case of crizotinib-resistant ALK-positive NSCLC, the rate of resistance due to mutations in the ALK kinase domain is typically reported in the range of 35-40%.[31] In response to causes of crizotinib treatment failure, next-generation ALK/ROS1TKIs are being developed.

The second-generation ALK inhibitors, which have demonstrated activity in a crizotinib-refractory or resistant treatment setting, may have the potential for even greater activity in treatment-naïve patients. Data from both alectinib[1,21] and ceritinib[25] have shown that using these more potent agents in the first-line advanced ALK-positive NSCLC treatment setting may exceed the median progression-free survival (PFS) time for crizotinib.

Lorlatinib is a selective, brain-penetrant ALK TKI with potent activity against ALK and ROS1 fusions, including those harboring resistance mutations. Lorlatinib has demonstrated clinically meaningful anti-tumor activity in patients with brain metastases after treatment with ALK inhibitors including crizotinib.[30] Further, lorlatinib appears to be the only ALK TKI active against certain mutations that are the most difficult to inhibit, such as the G1202R mutation.

Lorlatinib has the potential to improve PFS in the treatment-naïve advanced ALK-positive NSCLC treatment setting based on its greater potency against ALK and its broad coverage against all known single point mutations that mediate resistance to crizotinib and second-generation ALK inhibitors.[29]

STUDY OBJECTIVES and ENDPOINTS

Primary Objective

- To demonstrate that lorlatinib as a single agent (Arm A) is superior to crizotinib alone (Arm B) in prolonging progression-free survival (PFS) in advanced ALK-positive NSCLC patients who are treatment naïve.

Secondary Objectives:

- To compare Arm A with Arm B in treatment-naïve advanced ALK-positive NSCLC patients with respect to overall survival (OS);
- To evaluate the antitumor activity in each treatment arm;
- To evaluate the safety and tolerability in each treatment arm;
- To evaluate patient-reported outcomes (PROs) of health-related quality of life, disease/treatment-related symptoms of lung cancer, and general health status for each treatment arm;
- To evaluate candidate biomarkers of sensitivity or resistance to single-agent crizotinib or lorlatinib in pre-treatment tumor tissue;
- To evaluate candidate biomarkers of sensitivity or resistance to single-agent crizotinib or lorlatinib in peripheral blood.

Exploratory Objectives:

- [redacted]
- [redacted]
- [redacted]

Primary Endpoint:

- PFS based on Blinded Independent Central Review (BICR) assessment (RECIST v.1.1, see Appendix 3).

Secondary Endpoints:

- Efficacy: OS, PFS based on Investigator's assessment, Objective Response (OR) based on BICR and on Investigator's assessment; intracranial OR (IC-OR), IC-time to progression (IC-TTP), Duration of Response (DR) and IC-DR, Time to Tumor Response (TTR), and IC-TTRall by BICR (RECIST v. 1.1), and PFS2;

- Safety: Adverse Events (AEs), as graded by NCI CTCAE (National cancer Institute Common Terminology Criteria for Adverse Events) v.4.03; laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate) and body weight; electrocardiograms (ECGs); echocardiogram or MUGA (multigated acquisition) scan; ophthalmologic data;

- PRO as assessed by EORTC (European Organisation for Research and Treatment of Cancer) QLC-C30, EORTC QLQ-LC13, EQ-5D-5L;

- Tumor tissue biomarkers including, but not limited to, ALK gene rearrangement and/or mutations as measured by next-generation sequencing (NGS) and/or immunohistochemistry (IHC);

- Peripheral blood cfDNA (circulating free Deoxyribonucleic acid) biomarkers including, but not limited to, ALK gene rearrangement and/or ALK kinase domain mutations.

Exploratory Endpoints:

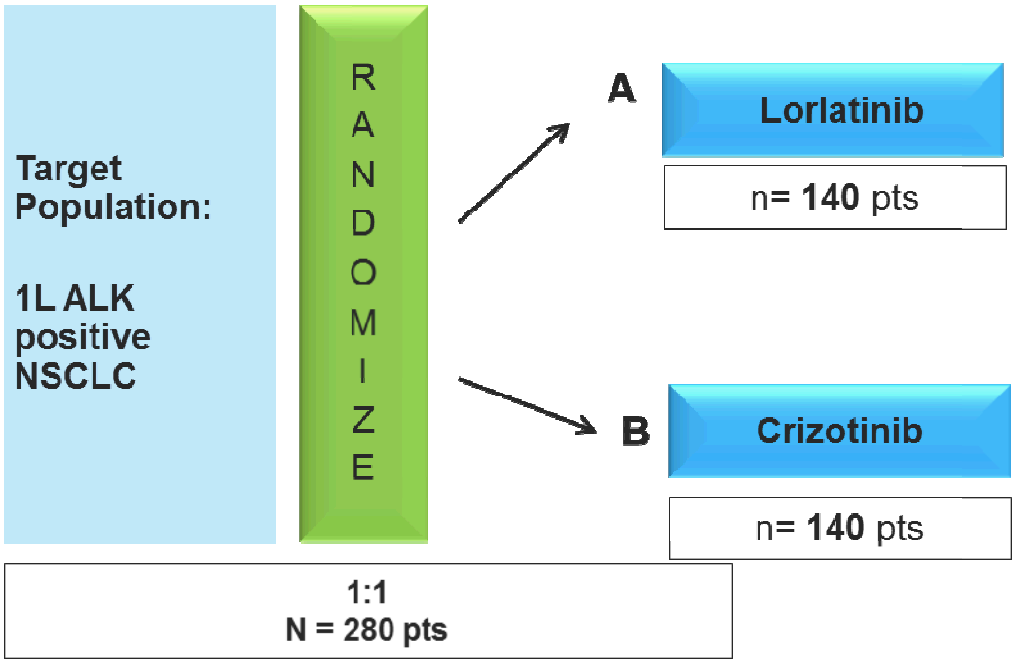
[redacted]

STUDY DESIGN

Study Overview

This is a Phase 3, multinational, multicenter (at approximately 160 sites), randomized, open-label, parallel 2-arm study in which approximately 280 previously untreated patients with advanced ALK-positive NSCLC were to be randomized 1:1 to receive lorlatinib monotherapy or crizotinib monotherapy according to the study design illustrated in Figure 1 below (296 patients were actually randomized).

Figure 1. Study B7461006 Design



- Patients will be stratified according to:
  - Presence of brain metastases (Yes vs. No);
  - Ethnic origin (Asian vs. non-Asian).
- Crossover between treatment arms will not be permitted.

Study Treatments

This study was to randomize 280 patients in a 1:1 ratio to receive either:

- Arm A: Lorlatinib monotherapy at the Recommended Phase 2 dose (RP2D) of 100 mg QD (quaque die; every day), administered as 4 x 25 mg oral tablets, continuously; or
- Arm B: Crizotinib monotherapy at the registered starting dose of 250 mg BID, administered as 1 x 250 mg oral capsules, twice daily, continuously.
  - Each cycle duration will be 28 days.

Study treatment may continue until confirmed disease progression assessed by BICR, patient refusal, patient lost to follow-up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first.

Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer.

Sample Size Determination

The primary objective of this study is to demonstrate that lorlatinib (Arm A) is superior to crizotinib (Arm B) in prolonging PFS by BICR assessment per RECIST v1.1. A key secondary objective of the study is to demonstrate that lorlatinib is superior to crizotinib in prolonging OS.

The study is designed to test H_0: $HR_{PFS} \geq 1$ vs. H_A: $HR_{PFS} < 1$, where HR_{PFS} is the hazard ratio (Arm A/Arm B) of PFS.

Approximately 280 patients (140 in each arm) were to be randomized using a 1:1 ratio stratified by presence of brain metastases and ethnic origin. As of 28 February, 2019 enrollment was closed with 296 patients randomized. One hundred seventy seven (177) PFS events will be required to have at least 90% power to detect a hazard ratio (HR) of 0.611 using a one-sided stratified log-rank test at a significance level of 0.025, and a 2-look group-sequential design with a Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries

The planned sample size was determined based on the assumption of a HR of 0.611 under the alternative hypothesis which, under an exponential model, assumes a median PFS of 11 months in the crizotinib arm and 18 months in the lorlatinib arm. CCI [redacted] The sample size further assumed a 15% drop-out rate within each treatment arm at 30 months and a non-uniform patient accrual over approximately 15 months and follow-up after the last patient is randomized of approximately 18 months

This sample size will also allow comparison of OS between the 2 treatment arms, provided that superiority of lorlatinib over crizotinib with respect to PFS has been demonstrated. If the true HR is 0.70 under the alternative hypothesis (under an exponential model, assumes median OS of 48 months on the crizotinib arm and 68.6 months on the lorlatinib arm), a total of 198 deaths will be required to have 70% power using a one-sided stratified log-rank test at a significance level of 0.025, and a 3-look group-sequential design with Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries.

These calculations further assumed a 15% drop-out rate for OS on either treatment arm at 120 months and a follow-up of approximately 110 months after the last patient is randomized.

SCHEDULE OF ACTIVITIES (SOA)

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and 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 patient.

		CYCLE 1 28 days			**CYCLE 2 28 days**	**CYCLES ≥3 (28 days per cycle)**	**END of TREATMENT (EOT)/FOLLOW-UP**		
Visit Identifier[a]	**Screening**[1] **(≤28 days prior to randomization)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment/ Withdrawal**[30]	**Post-Treatment Follow-Up**[31] **(every 4 weeks until PD)**	**Survival Follow-Up**[32] **(every 4 months up to 3 years, then every 6 months thereafter)**
Visit Time Window (days)	N/A		±1	±1	±2	±2	±3	±7	±7
Informed consent[2]	X								
Tumor history, including ALK status determination[3]	X								
Medical/oncological history (including prior medications and smoking history)	X								
Physical examination	X (full PE at screening only)	X			X	X	X	X	
Baseline signs and symptoms[4]		X							
Ophthalmologic examination[5]	X	To be repeated during the study in case of visual disturbances CTCAE grade increase, or as clinically indicated							
Height	X								
Weight[6]	X	X			X	X			
Vital signs[6]		X	X	X	X	X	X	X	

		CYCLE 1 28 days			CYCLE 2 28 days	CYCLES ≥3 (28 days per cycle)	END of TREATMENT (EOT)/FOLLOW-UP		
Visit Identifier[a]	**Screening**[1] **(≤28 days prior to randomization)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment/ Withdrawal**[30]	**Post-Treatment Follow-Up**[31] **(every 4 weeks until PD)**	**Survival Follow-Up**[32] **(every 4 months up to 3 years, then every 6 months thereafter)**
Visit Time Window (days)	N/A		±1	±1	±2	±2	±3	±7	±7
ECOG performance status[7]	X	X			X	X	X		
Contraception check[8]	X	X	X	X	X	X	X	X	
Laboratory									
Hematology[9]	X	X(- 7 days)	X	X	X	X	X	X	
Blood Chemistry[10]	X	X (-7 days)	X	X	X	X	X	X	
HBV, HCV (if applicable)	X								
Lipids[11]	X	X(- 7 days)	X	X	X	X	X	X (at 30 days)	
Coagulation[12]	X	X (-7 Days)			X	X	X	X	
Urinalysis[13]	X	X(-7 days)			(X)	(X)	X	X	
Pregnancy test[14]	X	X			X	X	X		
Triplicate (12-lead) ECGs[15]	X	X (pre and 1-4 hs post dose for Arm A and pre-dose for Arm B)	X (1-4 hs post dose for Arm A only)	X(1-4 hs post dose for Arm A only)	X(1-4 hs post dose for Arm A only and 2-6 hs post dose for Arm B)	X (single reading, pre-dose, on Day 1 of every other cycle for both Arms)	X (Triplicate ECG for both Arms)		
LVEF assessment (Echocardiogram or MUGA scan)[16]	X	X (pre- dose- not to be repeated if normal and performed <2 weeks prior to randomization)				X (pre-dose, on Day 1 of every other cycle; a time window of 1 week prior to Day 1 is permitted)	X		

		CYCLE 1 28 days			CYCLE 2 28 days	CYCLES ≥3 (28 days per cycle)	END of TREATMENT (EOT)/FOLLOW-UP		
Visit Identifier[a]	**Screening**[1] **(≤28 days prior to randomization)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment/ Withdrawal**[30]	**Post-Treatment Follow-Up**[31] **(every 4 weeks until PD)**	**Survival Follow-Up**[32] **(every 4 months up to 3 years, then every 6 months thereafter)**
Visit Time Window (days)	N/A		±1	±1	±2	±2	±3	±7	±7
For France and Germany only: Transthoracic echocardiogram (TTE) to assess PAP and right heart function.(refer to Section 7.4.6	X	X (pre-dose- not to be repeated if normal and performed <2 weeks prior to randomization)				X (at least every 6 months during treatment)	X (to be performed only if patient received at least 3 months of study drug treatment and if the last previous TTE assessment was performed more than 4 weeks before)		
Randomization and Treatment									
Randomization[17]		X							
Arm A: lorlatinib		orally on a continuous QD dosing schedule							
Arm B: crizotinib		orally on a continuous BID dosing schedule							

		CYCLE 1 28 days			CYCLE 2 28 days	CYCLES ≥3 (28 days per cycle)	END of TREATMENT (EOT)/FOLLOW-UP		
Visit Identifier[a]	**Screening[1] (≤28 days prior to randomization)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment/ Withdrawal[30]**	**Post-Treatment Follow-Up[31] (every 4 weeks until PD)**	**Survival Follow-Up[32] (every 4 months up to 3 years, then every 6 months thereafter)**
Visit Time Window (days)	N/A		±1	±1	±2	±2	±3	±7	±7
Tumor Assessments									
CT (Computed Tomography) or MRI (Magnetic Resonance Imaging) scan[18]	X	• every 8 weeks (±1 week) since randomization for CT or MRI scan. • every 16 weeks (+1 week) for Bone Scan/MRI **only** if evidence of bone metastases is observed at baseline.					X	X (every 8 weeks, ±1 week, until PD; for bone scan/MRI every 16 weeks ±1 week, until PD **only** if evidence of bone metastases is observed at baseline.	
Diagnostic Cerebrospinal Fluid [redacted][19]	X	To be repeated as clinically indicated and if clinically safe and feasible							
Other Clinical Assessments									
Serious and non-serious adverse event monitoring[20]	X	→	→		→	→	→	→	
Concomitant medications and non-drug supportive interventions[21]	X	X	→		→	→	→	→	X (subsequent anticancer treatment)
PRO Assessment[22]		X			X	X	X	X (only if patient visits the clinic)	
Mood Assessment[23]		X			X	X (up to Cycle 6 and then Day 1 of every other cycle)	X		

		CYCLE 1 28 days			CYCLE 2 28 days	CYCLES ≥3 (28 days per cycle)	END of TREATMENT (EOT)/FOLLOW-UP		
Visit Identifier[a]	**Screening[1] (≤28 days prior to randomization)**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment/ Withdrawal[30]**	**Post-Treatment Follow-Up[31] (every 4 weeks until PD)**	**Survival Follow-Up[32] (every 4 months up to 3 years, then every 6 months thereafter)**
Visit Time Window (days)	N/A		±1	±1	±2	±2	±3	±7	±7
Suicidal Ideation and Behavior[24]		X			X	X (up to Cycle 6 and then Day 1 of every other cycle)	X		
Survival status[31]									X
Other Samples									
Archival tumor tissue specimen[25]	X								
De Novo tumor specimens[26]	(X)						(X)		
CCI [redacted]	[redacted]				[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]					[redacted]	[redacted]		
[redacted]	[redacted]					[redacted]			

a. Day relative to start of study treatment (Day 1 of Cycle 1).

Abbreviations: → = ongoing/continuous event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; MUGA = Multigate acquisition; TTE = Transthoracic echocardiogram; CT = computed tomography; MRI = Magnetic Resonance Imaging; EORTC = European Organisation for Research and Treatment of Cancer; PD = Progression of Disease; ALK = anaplastic lymphoma kinase; PE = Physical examination; CTCAE = Common Terminology Criteria for Adverse Events; HBV = Hepatitis B Virus; HCV = Hepatitis C Virus; PRO = Patient-reported Outcome; QD = Quaque Die (every day); BID = Bis in Die (twice daily); CCI [redacted]; N/A = Not Applicable; PAP =Pulmonary arterial pressure

Footnotes:

(X) refer to specific footnote when the assessment may be optional/repeat assessment might not be required.

Acceptable time windows for performing each assessment are described in the column headers.

1. **Screening**: To be obtained within 28 days prior to randomization. Available results for assessements that have been performed prior to informed consent being obtained as part of routine standard of care (laboratory tests or tumor imaging scans) may be used to determine patient eligibility, provided they have been performed within the required timing (that is 7 days prior randomization for laboratory tests or 28 days prior randomization for tumor imaging).
2. **Informed Consent**: Must be obtained prior to undergoing any study-specific procedures. Informed consent for use of tissue for other CCI research or diagnostic development must also be obtained. Molecular Presceening Informed Consent must also be obtained in case the ALK status determination is not already available or has been performed through a test different from the required Ventana ALK (D5F3). IHC test performed on the ULTRA or XT platforms are acceptable, while tests performed on the GX platform cannot be accepted.
3. Prescreening activities to determine ALK status will be performed as needed:
   a. Patients who have historical results available showing ALK-positivity through Ventana ALK D5F3 CDx(Companion Diagnostics) test can proceed with the screening assessments. Available pathological reports must be prospectively collected and sent to Pfizer for confirmation of patient eligibility.
   b. Patients who have historical results available showing ALK-positivity through a non-Ventana ALK D5F3 CDx test can start the screening assessments while waiting for the Ventana ALK D5F3 CDx assay to be performed. Re -testing time should be in the 28 days time window.
   c. Patients who do not have historical results available must undergo a pre-screening Ventana ALK D5F3 CDx test and, if positive, can start the screening assessments.
   Please refer to Section 6.1.1.1 for additional details.
4. Baseline Signs and Symptoms: Patients will be asked about any signs and symptoms experienced and present pre-dose on Day 1 of Cycle 1.
5. Ophthalmologic Examination (right and left eye): Includes best corrected visual acuity, and refractive error slit lamp biomicroscopy and fundoscopy, and should be performed by an ophthalmologist. Testing will be performed at screening and should be repeated during the study whenever a vision disorder AE is observed or CTCAE grade change occurs from the previous visit (more frequent examinations may be performed based on local requirement).
6. Vital Signs: Blood pressure and pulse rate to be recorded in sitting position after 5 min rest. Body weight to be recorded on Day 1 of each cycle.
7. Performance Status: According to Eastern Cooperative Oncology Group (ECOG) classification (see Appendix 2).
8. Contraception Check: Male patients who are able to father children and female patients who are of childbearing potential will need to follow the contraception guidelines in Section 4.3.1.
9. Hematology: Required tests are listed in the Appendix 4 of the protocol. Not to be repeated at C1D1 if performed within 7 days before. May also be performed when clinically indicated (results to be entered in CRF as unplanned visit).
10. Blood Chemistry: Required tests are listed in Appendix 4 of the protocol. Not to be repeated at C1D1 if performed within 7 days before. May also be performed when clinically indicated (results to be entered in CRF as unplanned visit).
11. Lipids: Required tests are listed in the Appendix 4 of the protocol. Not to be repeated at C1D1 if performed within 7 days before. May also be performed when clinically indicated. (results to be entered in CRF as unplanned visit).
12. Coagulation: Required tests are listed in the Appendix 4 of the protocol. Not to be repeated at C1D1 if performed within 7 days before. May also be performed when clinically indicated (results to be entered in CRF as unplanned visit).
13. Urinalysis: Dipstick is acceptable. Microscopic analyses if dipstick abnormal and/or if this is the local standard. To be repeated as clinically indicated, for example upon diagnosis of renal cysts (more frequent assessment may be performed based on local requirement). Not to be repeated at C1D1 if performed within 7 days before.

14. Serum or Urine Pregnancy Test: For female patients of childbearing potential, a serum or urine pregnancy test, to be performed on two occasions prior to starting study therapy, once at the start of screening (serum) and once at the baseline visit (serum or urine), whose results must be available before investigational product administration. Pregnancy tests also routinely repeated at every cycle during the active treatment period, at the end of treatment and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests if requested by IRB/IECs or by local regulations.
15. Triplicate 12-Lead ECGs: At each time point, 3 consecutive 12-lead ECGs are to be performed approximately 2 minutes apart (or within 10 minutes, whichever is applicable). The ECG must occur prior to any blood sample collections or venipuncturing. Whenever it is not feasible, blood chemistry and hematology lab tests may be collected prior to the pre-dose ECG provided at least 30 minutes has elapsed between the venipunturing and the collection of the ECG. CCI [redacted] For Arm A (lorlatinib), ECGs are to be collected at pre-dose and 1-4 hours post-dose on Cycle 1 Day 1. ECGs will also be collected at 1-4 hours post-dose on Cycle 1 Day 8 and Day 15, and on Cycle 2 Day 1. Additional ECGs may be collected as clinically indicated. For Arm B (crizotinib), ECGs are to be collected at pre-dose on Cycle 1 Day 1. For Cycle 2 Day 1, the ECGs must be collected 2-6 hours after the morning dose. Additional ECGs at may be collected as clinically indicated. At End of Treatment/Withdrawal, triplicate ECGs are to be collected for both treatment arms. Additional ECG time points may be performed based on the emerging data. Single reading ECG are to be collected pre-dose on Day 1 of Cycle 3 and every other cycle thereafter.
16. LVEF Assessment: Echocardiogram or MUGA to be performed at Screening, at pre-dose (0 hour), on Cycle 1 Day 1 and on Day 1 of every other cycle thereafter, and at the EOT visit. The same method should be used at each time point. If the screening ECHO or MUGA is normal and has been performed within 2 weeks prior to randomization, there is no need to repeat this assessment at Day1 of Cycle 1. At subsequent visits a time window of 1 week prior to Day 1 of subsequent cycles will be permitted for the ECHO/MUGA assessment.
17. Randomization: Patient number and treatment arm allocation will be operated through an automated system. Study treatments to be initiated preferably on the randomization day but no later than 7 days after randomization.

    Arm A: lorlatinib administered orally, on a continuous QD dosing schedule, as described in Section 5.4.1.

    Arm B: crizotinib administered orally, on a continuous BID dosing schedule, as described in Section 5.4.2.
18. Tumor Assessments: To include all known or suspected disease sites. Baseline and on study imaging to include as mandatory exams: chest, abdomen, and pelvis CT or MRI scans; Brain MRI; Bone scan or MRI. Brain MRI (Gadolinium contrast enhanced) to be used for assessment of CNS lesions (even if brain metastases not suspected), with contingent slices of 1 mm for lesions with a minimum size of 5 mm – 10 mm in size, 5 mm for lesions greater than 10 mm. Bone scans (or bone MRI if preferred by investigator) to be performed at baseline for all patients and repeated every 16 weeks (+1 week) on study only if evidence of bone metastases is observed at baseline. For all tumor assessments, the method of assessment that was used at baseline should be the same method used throughout the study. CT or MRI scans to be done at every 8 weeks ±1 week (every 16 weeks for bone scans/MRI) starting from randomization while on treatment or post-treatment follow-up (until PD). Responses will be confirmed ≥4 weeks later. Tumor assessment should be repeated at the EOT visit if more than 8 weeks have passed since the last evaluation. Tumor assessments must continue until documented progression of disease by BICR. If a patient continues study treatment beyond disease progression confirmed by BICR, based on investigator judgement of clinical benefit, (eg, in case the intracranial lesions are not in progression) tumor assessment must continue to be performed every 8 weeks ±1 week (16 weeks ±1 week for Bone Scan/MRI if applicable). Patients who discontinue treatment without PD should be followed radiologically until PD is confirmed by BICR regardless of subsequent anti-cancer treatments. Assessment of response will be made using RECIST v.1.1. Assessment of response of measurable intracranial disease will be made using a modified version of RECIST v.1.1.[33]
19. Diagnostic Cerebrospinal Fluid (CSF) analysis is mandatory for patients with suspected or confirmed leptomeningeal disease/carcinomatous meningitis (LMD/CM) not visualized on MRI (optional for the remaining patients). To be performed at baseline, and if clinically safe and feasible, further CSF cytology will be performed as clinically indicated to assess anti-tumor response and to determine CCI [redacted] crizotinib concentrations. (Of note: if a patient is required to undergo a lumbar puncture while on study drug, an additional ~5 mL sample of CSF should be collected for determining CCI [redacted] crizotinib and its metabolite (for Arm B) concentrations. If a CSF sample is collected, CCI [redacted] Detailed collection procedures will be provided in the Study Manual).

20. Adverse Event (AE) Assessments: AEs should be documented and recorded at each visit using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. For AEs and Serious Adverse Events (SAEs), the active collection period to Pfizer or its designated representative begins from the time that the patient provides informed consent, through and including 28 calendar days after the last administration of the investigational product. If a patient begins a new anticancer therapy, the recording period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.
21. Concomitant Medications and Non-Drug Supportive Interventions: All concomitant medications and non-drug supportive interventions will be recorded in the CRF from 28 days prior to start of study treatment and up to 28 after the last dose of study treatment.
22. PRO Assessment: Patients must complete all EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L self-assessment questionnaires in the clinic as these cannot be taken home. All scheduled assessments of the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L must be completed in the clinic prior to any other study or medical procedures.
23. Mood Assessment: An assessment of mood via the Beck Depression Inventory II (BDI II) scale will be administered to patients prior to the first day of investigational drugs dosing (ie, Cycle 1 Day1) and then prior to dosing on Day 1 of Cycle 2 through –Cycle 6. After Cycle 6 Day 1, this test will be administered prior to dosing on Day 1 of every other cycle (ie, Cycle 8 Day 1, Cycle 10 Day 1, etc.) and at EOT.
24. Suicidal Ideation and Behavior: An assessment of suicidal ideation and behavior via the Columbia Suicide Severity Rating Scale (C- SSRS) will be administered to patients prior to the first day of investigational drugs dosing (ie, Cycle 1 Day1) and then prior to dosing on Day 1 of Cycle 2 through Cycle 6. After Cycle 6 Day 1, this test will be administered prior to dosing on Day 1 of every other cycle (ie, Cycle 8 Day 1, Cycle 10 Day 1, etc.) and at EOT.
25. Archival Tumor Tissue Specimens: All patients must provide a formalin-fixed paraffin-embedded (FFPE) archival tumor specimen, specifically a FFPE tissue block that contains sufficient tissue to generate at least 10 (preferably 15) unstained slides, each with tissue sections that are ~5-microns thick. If a FFPE tissue block cannot be provided, at least 10 (preferably 15) unbaked glass slides, each containing an unstained ~5-micron FFPE tissue section must be submitted. If archived FFPE tissue is not available, a de novo (fresh) tumor sample must be obtained in accordance with local institutional practice for tumor biopsies. Acquisition of archival or de novo tumor tissue is mandatory for patient enrollment. Archived or de novo tumor tissue from cytological sampling (eg, fine needle aspiration, pleural effusion, including FFPE block is acceptable at screening and can be submitted. Archived or de novo tumor tissue from bone metastasis (eg, bone biopsy specimen), is not adequate at screening and should not be submitted.
26. De Novo Tumor Specimens: De novo tumor core needle biopsy collection will be mandatory at screening if archival tissue is not available. CCI [redacted] Endobronchial Ultrasound Guided Transbronchial Core Needle biopsies are adequate. Pleural effusions (PE) cell pellets may substitute for tumor core biopsy as appropriate. Fine needle aspiration (FNA) samples (2-3 pass minimum prepared as FFPE cell block) should only be performed in the event a biopsy or pleural effusion cell pellet is not safe or feasible. Tumor tissue should be provided as a FFPE tumor tissue block containing sufficient tumor tissue to allow if possible for sectioning of at least 10 (preferably 15) slides each containing a ~5-micron tissue section. If local country regulations do not allow for tissue block to be submitted or if a tissue block cannot be provided, sites should provide if possible at least 10 (preferably 15) unbaked glass slides each containing a ~5-micron tissue section cut serially from the same block. Details for handling of these samples including processing, storage, and shipment will be provided in the Study Manual.

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30. End of Treatment (EOT) Visit: Obtain these assessments if not completed in the last week (Tumor assessment should be repeated a the EOT visit if more than 8 weeks have passed since the last evaluation.). EOT visit is usually scheduled for 28 days after the last dose of investigational product or when decision taken to provide alternative anti-cancer therapy whichever is sooner.
31. Post-Treatment Follow-Up Visits: Patients will return to undergo review of concomitant medications, laboratory tests, vital signs, and assessment for resolution of any treatment-related toxicity until PD or until the time of initiation of new anticancer treatment. At this point, patients continuing to experience treatment related toxicities will continue to be followed at least every 4 weeks (except for the tumor assessment which will be performed every 8 weeks ±1 week (every 16 weeks ± week for bone scan/MRI if applicable), until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Patients discontinuing treatment for reasons other than progression of disease will continue to perform tumor assessments until PD documented by BICR, regardless of subsequent anti-cancer treatments.
32. Survival Follow-Up: After discontinuation of study treatment, information on post-study survival status and subsequent anti-cancer treatment (including administration start and stop dates, reason for treatment discontinuation and date of disease progression, if applicable) will be collected every 4 months up to 3 years, then every 6 months until death, or patient withdrawal of consent or study closure (after the required number of OS events have been reported), whichever occurs first. Telephone contact is acceptable for patients refusing/unable to go back to the site.

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

PF-06463922 (lorlatinib) is an anaplastic lymphoma kinase (ALK) and c-ROS oncogene-1 (ROS1) receptor tyrosine kinase inhibitor that is currently being investigated in patients with previously untreated advanced ALK-positive non-small cell lung cancer (NSCLC).

The mechanism of actions of crizotinib and lorlatinib are described in Section 1.2.4 and Section 1.2.5, respectively.

1.2. Background and Rationale

1.2.1. NSCLC

NSCLC is the most common cause of fatal malignancy globally, most often diagnosed in advanced stages, where surgery and local radiotherapy are no longer curative or indicated.[1,2] Standard therapy in later stages of disease is primarily palliative in nature, involving the use of cytotoxic chemotherapy with or without radiation therapy and immunotherapy.[3,4,5]

In spite of these treatments, 5-year survival is only about 17% for advanced-stage NSCLC patients, highlighting the need for novel therapies and treatment regimens.[6,7]

Targeted therapies such as tyrosine kinase inhibitors (TKIs) may be used in advanced NSCLC patients who have tumors that harbor various alterations, including the fusion protein EML4-ALK. The first approved agent for anaplastic lymphoma kinase (ALK)-positive NSCLC was crizotinib. Although most patients with ALK-positive NSCLC derive substantial clinical benefit from crizotinib, some ALK-positive NSCLC patients will not derive any benefit (intrinsic resistance), while other patients who initially derive benefit will develop resistance (acquired resistance). In the case of crizotinib-resistant ALK-positive NSCLC, the rate of resistance due to mutations in the ALK kinase domain is typically reported in the range of 35-40%.[31]

1.2.2. ALK Alterations in NSCLC

A rearrangement within chromosome 2p resulting in the formation of a fusion gene product comprising portions of the echinoderm microtubule-associated protein-like-4 (EML4) gene and the ALK gene was discovered in 2007 in NSCLC cell lines and archived clinical specimens.[8] A subsequent series of studies have described 9 fusion variants of EML4-ALK plus additional but less common fusion partners with ALK.[9] Currently, there are at least 27 different ALK fusion variants reported in the literature, the majority of isoforms involve EML4-ALK. ALK-positive NSCLC patients, who represent between 3% and 5% of all NSCLC cases, tend to be young (average age 50 years at diagnosis), and light or never smokers.[10]

Oncogenic fusions of ALK and ROS1 define 2 distinct subsets of human lung adenocarcinomas,[8,11] and play essential roles in regulation of tumor cell survival, growth, and metastasis. Targeting ALK or ROS1 in these cancers provides a novel opportunity to selectively target cancer cells bearing ALK or ROS1 fusions that are implicated as causative oncogenic driver events in these patients' tumors.[12,13]

The first-generation ALK/ROS1/cMET inhibitor crizotinib (Xalkori®) has demonstrated impressive clinical benefit in ALK and ROS1 fusion-positive lung cancers[12,13] leading to the approval of crizotinib for the treatment of advanced ALK-positive NSCLC patients. The European Commission also approved a product label update to expand use of crizotinib to first-line treatment of adults with ALK-positive advanced NSCLC.[13] Thus, crizotinib has become the global standard of care (SOC) for patients with ALK-positive NSCLC.

1.2.3. Resistance Mechanisms

Although most patients with ALK-positive NSCLC derive substantial clinical benefit from crizotinib, some patients will not derive any benefit (intrinsic resistance), while most patients who initially derived benefit will eventually develop resistance (acquired resistance) to crizotinib.[14] Acquired ALK kinase domain mutations and/or brain metastases are two major relapse mechanisms to crizotinib therapy.[14,15,16] In the case of crizotinib-resistant ALK-positive NSCLC, the rate of resistance due to mutations in the ALK kinase domain is typically reported in the range of 35-40%.[16] Resistance to ALK TKIs may be related to gatekeeper mutations along with activation of bypass resistance mechanisms such as somatic variations in tumor response pathways. Multiple types of ALK kinase mutations have been identified in crizotinib-refractory or resistant patients.[16-19]

In response to these causes of crizotinib treatment failure, next-generation ALK/ROS1 TKIs are being developed.

The first of the second-generation ALK inhibitors to show a significant clinical activity has been ceritinib (ZYKADIA™).[20] Results from a global Phase 1 study led to the drug's accelerated approval for the treatment of NSCLC patients who progressed or were intolerant to crizotinib in US and Europe, based on tumor response and duration of response.

Alectinib (ALECENSA™) is a selective ALK inhibitor, has CNS (central nervous system) activity, and has shown clinical activity in both crizotinib-resistant and treatment-naïve patients. Alectinib is approved in Japan and has received accelerated approval in the US for the treatment of patients with ALK-positive NSCLC who have progressed or are intolerant to crizotinib.[23]

The second-generation ALK inhibitors, which have demonstrated activity in a crizotinib-refractory or resistant treatment setting, may have the potential for even greater activity in treatment-naïve patients. Data from both alectinib[1,21] and ceritinib[25] have shown that using these more potent agents in the first-line advanced ALK-positive NSCLC treatment setting may exceed the median PFS time for crizotinib.

The Phase 3 study J-ALEX of alectinib vs. crizotinib conducted in Japanese patients with ALK-positive NSCLC had been stopped early following a recommendation by an Independent Data Monitoring Committee, as the study met its primary endpoint at a pre-planned interim analysis.[1,21]

A separate Phase 3 study of alectinib compared with crizotinib in patients with treatment-naïve ALK-positive advanced NSCLC (ALEX) has just completed accrual with a total of 303 patients enrolled. The study Primary Completion Date that is the final data collection for the primary outcome measure is expected in March 2017.[24]

In the Phase 1/2 Study B7461001, lorlatinib demonstrated robust clinical activity in both ALK-positive and ROS1-positive NSCLC patients, most of whom had brain metastases and had received ≥1 prior ALK TKI. An objective response rate (ORR) of 46% was observed in patients who received ≥2 prior ALK TKI treatments. When considering the patients who received only 1 previous ALK TKI, the ORR was 57%.

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Significant intracranial responses were also observed, showing that lorlatinib can cross the blood–brain barrier to achieve clinically meaningful anti-tumor activity in patients with brain metastases after treatment with ALK inhibitors including crizotinib. Lorlatinib in fact showed an intracranial ORR of 31% when considering both target and non-target lesions and of 39% when considering the target lesions only.[30] Further, lorlatinib appears to be the only ALK TKI active against certain mutations that are the most difficult to inhibit, such as the G1202R mutation.

Lorlatinib, therefore, has the potential to improve PFS times in the treatment-naïve ALK-positive advanced NSCLC treatment setting based on its greater potency against ALK and its broader coverage against all known single point mutations that lead to resistance to crizotinib and second generation ALK inhibitors.[29]

1.2.4. Crizotinib (XALKORI®)

Crizotinib, which is used in this study as the comparator arm vs the experimental arms, is the SOC used to treat NSCLC that has spread to other parts of the body and is caused by a defect in the ALK gene. To date, crizotinib has received traditional or conditional approval for the treatment of patients with ALK-positive advanced NSCLC in many countries including the United States (US), Europe (EU), and Japan. Crizotinib has also received traditional approval for the treatment of patients with ROS1-positive advanced NSCLC in the US.

Crizotinib is a selective ATP-competitive small-molecule inhibitor of ALK, ROS1, RON (Recepteur d'Origine Nantais), and c-MET/Hepatocyte Growth Factor Receptor (HGFR) tyrosine kinases and their oncogenic variants (eg, ALK or ROS1 fusion proteins or c-MET/HGFR mutant variants). Consistent with this mechanism of action, crizotinib inhibited phosphorylation of c-MET/HGFR and selected ALK fusion or mutant variants in tumor cells both in vitro and in vivo, and RON and ROS1 in vitro. Crizotinib exhibited potent and selective growth inhibitory activity against tumor cells exhibiting translocation/inversion or selected mutations involving the ALK gene locus (EML4-ALK or nucleophosmin [NPM]-ALK fusion variants).

Oral dosing of crizotinib 250 mg twice daily (BID) showed plasma concentrations reach steady state within 15 days and remain stable. The mean apparent terminal half-life was 42 hours in cancer patients after a single dose. Crizotinib is absorbed with a peak plasma concentration occurring between 4 and 6 hours under fasted condition. Crizotinib is a substrate of P- glycoprotein and is predominately metabolized by CYP3A4/5. Elimination of crizotinib was related to its hepatic, and possibly gastrointestinal, metabolism with a mean of 63.1% of [^{14}C] crizotinib excreted in the feces and 22.2% in the urine (crizotinib Investigator's Brochure [IB]).

Overall, the adverse events (AEs) reported for crizotinib in clinical studies were considered generally tolerable and manageable. For single-agent crizotinib, the most common AEs (≥20% of patients) reported as of March 2015 from 1761 (95.7%) of the 1840 patients with advanced NSCLC as treatment-related were vision disorders (60.4%), nausea (49.1%), diarrhea (48.1%), vomiting (43.9%), edema (38.1%), constipation (32.4%), elevated transaminases (30.4%), fatigue (21%), and neutropenia (20.4%). The majority of AEs were Grades 1 or 2 in severity, while treatment-related AEs of Grades 3, 4, or 5 in severity were observed among 701 (38.1%) advanced NSCLC patients who received at least 1 dose of single-agent crizotinib 250 mg BID. The most common (≥2%) Grade 3 treatment-related AEs were neutropenia, elevated transaminases, hypophosphatemia, lymphopenia, leukopenia, and fatigue. The most common (≥1%) Grade 4 treatment-related AEs were neutropenia, and elevated transaminases. The Grade 5 treatment-related AEs were interstitial lung disease (ILD) (0.4%), death (0.2%), and pneumonia, hepatotoxicity, lung infection, disseminated intravascular coagulation, arrhythmia, dyspnea, pulmonary embolism and deep vein thrombosis (0.1% each) (crizotinib IB).

There are special warnings regarding crizotinib use that must be considered and are described in detail in the crizotinib IB. Fatal drug-induced hepatotoxicity occurred in less than 1% of all patients treated with crizotinib in clinical trials and usually appeared within the first 2 months of therapy. Other warnings are pneumonitis/ILD and QTc prolongation, which both occurred in fewer than 2% of patients, and bradycardia which occurred in approximately 6% of patients. Specific management for these events is described in Table 5.

Clinical trials of crizotinib showed high rates of objective tumor response, and the responses were rapid and durable (Studies A8081001 and A8081005). In Study A8081007 (PROFILE 1007), second-line treatment of advanced ALK-positive NSCLC patients with crizotinib (after initial platinum-based chemotherapy) demonstrated a significant improvement in

median PFS when compared to chemotherapy (pemetrexed or docetaxel monotherapy) of 7.7 months vs. 3.0 months, respectively (HR 0.487; 95% CI (confidence interval): 0.371, 0.638; P <0.0001). The ORRs were 65% (95% CI: 58, 72) with crizotinib, as compared with 20% (95% CI: 14, 26) with chemotherapy (p<0.001). The median DR was 32.1 weeks with crizotinib (95% CI: 2.1, 72.4), as compared to 24.4 weeks with chemotherapy (95% CI: 3.0, 43.6).[14]

Validated questionnaires (EORTC QLQ-C30 and QLQ-LC13) showed a significantly greater improvement in patient-reported lung cancer symptoms and global quality of life receiving crizotinib as compared with chemotherapy.[14]

The first-line use of crizotinib was evaluated in Study A8081014 (PROFILE 1014) as compared with chemotherapy. The treatment of patients with ALK-positive NSCLC with crizotinib demonstrated significant improvement in median PFS and ORR when compared with pemetrexed plus platinum chemotherapy (median PFS: 10.9 months vs. 7.0 months, respectively; HR 0.454; 95% CI: 0.346, 0.596; p <0.001; ORR: 74% vs. 45%, respectively; p <0.001). The DR was 11.3 months with crizotinib (95% CI: 8.1, 13.8) as compared with 5.3 months (95% CI: 4.1, 5.8).[27]

Additional improvements were seen in the use of crizotinib over chemotherapy in patients with ROS1-positive advanced NSCLC.[28]

Complete information for crizotinib may be found in the single reference safety document (SRSD) which, for this drug, is the crizotinib core data sheet (CDS).

1.2.5. Lorlatinib (PF-06463922)

The lorlatinib program was initiated with the aim to develop a next-generation ALK inhibitor that is more potent than crizotinib, capable of inhibiting the catalytic activity of ALK-resistant mutants, and able to cross the blood-brain barrier.[29]

Lorlatinib is a potent and selective, macrocyclic, ATP competitive small molecule inhibitor of ALK and ROS1 receptor tyrosine kinases. It is orally available, brain penetrating, and able to inhibit all clinically reported ALK kinase domain mutations responsible for resistance to crizotinib.[30]

This drug is currently in clinical development and is being investigated for the treatment of ALK-positive or ROS1-positive advanced NSCLC. Lorlatinib has so far had substantial efficacy results which are described in more detail in Section 1.2.5.3.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the lorlatinib IB.

1.2.5.1. Preclinical Data

Lorlatinib has been studied in a variety of in vitro and in vivo model systems to determine potency for inhibition of ALK or ROS1 tyrosine kinase activity, kinase selectivity, antitumor efficacy, pharmacokinetic (PK)/pharmacodynamic (PD) relationships, and mechanism of action.

In vitro, lorlatinib demonstrated potent, concentration-dependent inhibition of catalytic activities of ALK, ALK mutants, and ROS1 kinases in recombinant enzyme and cell-based assays. PF-06463922 also inhibited ALK and ROS1 dependent oncogenic functions in human NSCLC cell lines and demonstrated potent and selective growth inhibitory activity and induced apoptosis in tumor cell lines exhibiting either non-mutant ALK and ROS1 fusion variants or mutant ALK fusions that are resistant to crizotinib treatment.

In vivo, lorlatinib demonstrated marked cytoreductive activity in mice bearing tumor xenografts that express ALK or ROS1 fusion variants, including the crizotinib-resistant EML4-ALK^{L1196M} or EML4-ALK^{G1269A} mutations. Lorlatinib treatment significantly reduced tumor size and prolonged animal survival in the orthotopic brain models (EML4-ALK and EML4-ALK^{L1196M}) in mice. The antitumor efficacy of lorlatinib was dose-dependent and demonstrated a strong correlation to inhibition of ALK or ROS1 phosphorylation.

Detailed information on PK/PD modeling, ADME (Absorption, Distribution, Metabolism and Elimination), and CYP enzymes inhibition can be found in the lorlatinib IB.

As described in the lorlatinib IB, the nonclinical safety profile of PF-06463922 has been adequately characterized to support continued clinical trials in advanced cancer indications.

1.2.5.2. Teratogenicity

Preliminary developmental toxicity studies using lorlatinib have been completed in rats and rabbits. Embryonic and fetal toxicity (including embryo lethality, fewer and smaller viable fetuses with some external and visceral malformations) was observed in both species at all doses, where the low dose was projected to yield similar exposure as the RP2D of 100 mg once daily. Based on the study results, lorlatinib induces embryonic and fetal toxicity in animals, and the current safety measures in the clinical development program for lorlatinib to prevent pregnancy should remain in place.

Additional information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the IB.

1.2.5.3. Clinical Data

The first-in-human Study B7461001 with lorlatinib is a Phase 1/2, dose escalation, safety, PK, PD, and anti-cancer efficacy exploration study of this investigational drug as a single agent in patients with advanced ALK-positive or ROS1-positive NSCLC.

This clinical study consists of 2 parts: both parts - Phase 1 and Phase 2 portion - have completed the enrollment (329 patients have been enrolled, 54 in the Phase 1 portion and 275 in the Phase 2).

As of the data cutoff date of 5 May 2016 a total of 165 patients have been treated with lorlatinib, 54 in the Phase 1 portion and 111 in the Phase 2 portion.

Maximum Tolerated Dose (MTD) Determination

The Phase 1 portion of the study was designed to estimate the maximum tolerated dose (MTD) for lorlatinib as a single agent in patients with advanced ALK-positive or advanced ROS1-positive NSCLC with or without asymptomatic CNS metastases. As part of this study, the food effect was also tested in a limited subset of patients, as well as the midazolam (MDZ) drug-drug interaction (DDI), given at steady-state, to evaluate the effect of lorlatinib on CYP3A inhibition/induction.

The MTD estimate was defined as the highest dose level associated with 33% of patients experiencing a dose-limiting toxicity (DLT). Due to the discreteness of the dose levels and in the interest of patient safety, the estimated MTD was defined as the highest dose level with a DLT rate <0.33. The primary endpoint of first-cycle DLTs was defined with pre-specified severity based upon predicted target organ toxicity in hematologic and non-hematologic system organ classes. Additionally, the inability to obtain sufficient drug administration due to treatment-related toxicities (but not of DLT severity) was also considered a DLT.

Importantly, the neurocognitive AEs observed in the first portion of dose escalation were late appearing and considered undesirable, even though most did not meet the definition of a DLT. Thus, the RP2D was determined based on the entirety of the safety, efficacy, and clinical pharmacology data instead of a formal DLT and MTD determination.

To date, lorlatinib has been administered across 7 different daily (QD) doses (10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, and 200 mg) and 3 different BID doses (35 mg BID, 75 mg BID, and 100 mg BID). A continual reassessment method (CRM) model was used in the dose escalation portion of Phase 1 to determine which doses to test based on the dose-limiting toxicities (DLTs) observed during Cycle 1.

A food effect cohort was tested at 100 mg QD (3 patients in fed/fasted state and 3 patients in fasted/fed state). Finally, a cerebrospinal fluid (CSF) sampling cohort was tested at 100 mg QD to obtain preliminary information about lorlatinib penetration into the brain.

Taken together, the 100 mg QD dose was chosen as the RP2D based on the entirety of the safety, efficacy, and clinical pharmacology data.

The Phase 2 portion was designed to evaluate the anti-cancer activity of single-agent lorlatinib administered at the dose of 100 mg QD in different cohorts of patients with advanced ALK-positive and with advanced ROS1-positive NSCLC. This will also allow characterization of the safety, PK, and PD profiles of single-agent lorlatinib at the RP2D determined at the end of Phase 1.

Safety

Overall, lorlatinib was well tolerated in Phase 1. As of the data cutoff date of 5 May 2016, the most commonly occurring treatment-related AEs across all of the doses tested were hypercholesterolemia (68.5%), CNS effects (44.4%), peripheral edema and hypertriglyceridemia (37% each), and peripheral neuropathy (35.2%). The most frequently occurring treatment-related Grade ≥3 AEs were hypercholesterolemia (11.1%) and hypertriglyceridemia (5.6%), for which treatment with a statin is recommended at the first signs of elevated (Grade 1) cholesterol and/or triglycerides.[30]

The Phase 2 portion confirmed the safety profile of the Phase 1 portion, with the most commonly occurring treatment-related AEs including hypercholesterolemia in 75.7% of patients, hypertriglyceridemia reported in 57.7% of patients, and CNS effects reported in 30.6% of patients. The most commonly reported Grade ≥3 treatment-related AEs were hypercholesterolemia (15.3%) and hypertriglyceridemia (10.8%). There were no Grade 5 treatment-related treatment-emergent AEs (TEAEs) reported.

Temporary dosing interruptions and dose reductions were reported in 18 (33.3%) and 13 (24.1%) patients, respectively in the Phase 1 portion and in 13 (11.7%) and 11 (9.9%) of patients respectively in the Phase 2 portion. Most of these delays and reductions occurred at doses higher than 100 mg QD and the most common reasons for dosing interruption and/or dose reduction at these higher doses were hypercholesterolemia and CNS effects.

Treatment-related CNS effects have been observed in 24 (44.4%) Phase 1 patients and 34 (31%) Phase 2 patients. The most common treatment-related CNS effects reported in the Phase 1 portion was Slow speech, occurring in 9.3% of patients. The most common treatment-related CNS effects individual AEs reported in the Phase 2 portion have been Dizziness and Memory impairment, each occurring in 4.5% of patients. The CNS effects reported in both Phase 1 and Phase 2 portions have been generally considered mild (Grade 1 and Grade 2) in severity and transient and improved upon dose delay and/or dose reduction. No Grade 4 or 5 CNS effects have been reported in the Phase 1 or Phase 2 portions.

A more detailed evaluation of CNS effects is ongoing in the Phase 2 portion by routine assessment of cognition, mood, and suicidality through a computerized test (using laptops provided by Cogstate). Based on the preliminary results observed, the assessments in this randomized Phase 3 study will be limited to mood and suicidality.

Treatment-related peripheral neuropathy events have been observed in 19 (35.2%) Phase 1 patients and 14 (12.6%) Phase 2 patients. The most commonly reported individual TEAE was Neuropathy peripheral, reported in 12 (22.2) Phase 1 patients and 6 (5.4%) Phase 2 patients. Similar to CNS effects, the peripheral neuropathy TEAEs were generally mild in severity and improved upon dose delay and/or dose reduction. No Grade ≥3 peripheral neuropathy TEAEs have been reported.

A total of 6 patients had treatment-related serious adverse events (SAEs) in the Phase 1 portion; 4 had CNS events that included Grade 2 hallucinations and seizure and Grade 3 delirium and mental status changes. In addition, 1 patient had Grade 3 dermatomyositis, and 1 patient had Grade 3 lipase increased. No Grade 4 or Grade 5 treatment-related SAEs were reported. There were neither any AEs that were associated with permanent treatment discontinuation, nor any treatment-related deaths (lorlatinib IB). In the Phase 2 portion, 9 patients had treatment-related SAEs, including 2 cases of acute respiratory failure of Grade 3 and 4 severity, respectively; 1 case of Grade 4 hypercholesterolemia; Grade 3 gastritis, pancreatitis, pneumonia, and mental status changes; 1 case of Grade 2 presyncope; and 1 case of Grade 1 worsening nausea.

As of the data cutoff date, a total of 20 deaths have been reported in Phase 1 and 5 deaths have been reported in Phase 2; none of these 25 events were attributed to lorlatinib.

Efficacy

In terms of preliminary efficacy in Phase 1, lorlatinib demonstrated promising clinical activity, although these patients represent a heterogeneous mix of driver mutations, prior treatments, and dose levels at which they were treated.

There were 25 Phase 1 patients still receiving treatment as of the data cutoff date. Among 53 patients evaluable for efficacy as of the data cutoff date (05 May 2016), the ORR was 47.2% and included 3 (5.7%) confirmed complete responses (CR), and 22 (41.5%) confirmed partial responses (PR). In addition, 10 (18.9%) patients had stable disease (SD) as their best overall response.

Thirty-nine (72%) out of 54 patients enrolled in the Phase 1 portion had CNS metastases at study entry. Of the 39 patients evaluable for intracranial response at the time of the data cutoff date, 10 (25.6%) patients had a confirmed CR and 4 (10.3%) patients had a confirmed PR, resulting in an intracranial ORR of 35.9%. Further, 13 (33.3%) patients had SD as their best overall response.

Overall Results

Taken together, these preliminary efficacy results from Phase 1 suggest substantial anti-tumor activity and brain penetration which are being further characterized in Phase 2.

Although the AE profile of lorlatinib in Phase 1 consists mostly of laboratory abnormalities, none of which were dose limiting, there was concern over the appearance of CNS effects particularly at doses higher than 100 mg QD, which were considered intolerable to some patients and were a cause for dose modification (ie, dosing interruption and/or dose reduction). Overall, 100 mg QD was a well-tolerated dose. None of the Phase 1 patients at this dose required dose reduction. Dose delays did occur in 44.4% of patients, in 33.3 % of them due to treatment-related AEs. These dose delays were not attributed to CNS effects, but rather to hypercholesterolemia or hypertriglyceridemia, or to disease-related events.

Additionally, based on the PK data observed, simulated patient exposure suggested that the 100 mg QD dose was the lowest dose exceeding the lorlatinib Ceff of 150 ng/mL during the majority of the dosing cycle once steady state was reached. The Ceff of 150 ng/mL was a concentration predicted to result in 80% tumor growth inhibition of the ALK G1202R resistance mutation. Further, lorlatinib demonstrated response rates of 47% (including a 36% intracranial response rate), which indicated that this compound is active both inside and outside the brain.

Taken together, the 100 mg QD dose was chosen as the RP2D based on the entirety of the safety, efficacy, and clinical pharmacology data.

Lorlatinib received food and Drug (FDA) orphan drug designation for the treatment of ALK positive or ROS1 positive NSCLC in June 2015.

1.2.6. Study Rationale

In response to causes of crizotinib treatment failure, next-generation ALK/ROS1 TKIs are being developed. Lorlatinib is a selective, brain penetrant ALK TKI with potent activity against ALK and ROS1 fusions, including those harboring resistance mutations. Crizotinib is the current SOC in the treatment of patients with advanced ALK-positive NSCLC, who have not received any prior NSCLC treatment, including molecularly targeted agents, angiogenesis inhibitors, immunotherapy, or chemotherapy).

Lorlatinib has the potential to improve PFS in this setting based on its greater potency against ALK and its broad coverage against all known resistance mutations to crizotinib and second-generation ALK inhibitors.[29] Additionally, lorlatinib has the ability to cross the blood-brain barrier with demonstrated clinically meaningful anti-tumor activity in patients with brain metastases after treatment with ALK inhibitors including crizotinib.[30]

Lorlatinib is expected to have greater efficacy than the SOC, and thus will be tested against crizotinib in the previously untreated advanced ALK-positive NSCLC treatment setting. Additionally, competitor ALK TKI data suggest that use of more potent agents in the first-line treatment setting will lead to prolonged PFS. Both alectinib[21] and ceritinib,[25] in fact, have shown longer median PFS times in the treatment-naïve advanced ALK-positive NSCLC population than that observed in patients with crizotinib-refractory or resistant disease.

Data on resistance mutations and mechanisms are still emerging from the clinic; there may be other resistance mutations and mechanisms that will not be sensitive to ALK inhibition. To further expand on biomarker data currently being collected in the ongoing Phase 2 study, this Phase 3 study will also evaluate candidate predictive biomarkers of sensitivity or resistance to single-agent crizotinib or lorlatinib in pretreatment tumor tissue and evaluate blood-based molecular markers of response and resistance to single-agent crizotinib or lorlatinib.

1.2.7. Rationale for Starting Dosing Regimens

- Arm A: Lorlatinib starting dosing regimen will be 100 mg QD which was chosen as the RP2D based on the entirety of the safety, efficacy, and clinical pharmacology data available.

- Arm B: Crizotinib starting dosing regimen will be 250 mg BID. This dose is the approved starting dose for treatment of ALK-positive metastatic NSCLC according to the crizotinib product label.

1.2.8. Summary of Benefit/Risk Assessment

An evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC (cf. Article 6(3)(b) of Directive 2001/20/EC) has been conducted.

For single-agent lorlatinib, based on the non-clinical results and the clinical data available to date from the Phase 1/2 clinical trial, the conduct of this study with the proposed lorlatinib dosing regimen is considered justifiable.

Lorlatinib treatment significantly reduced the tumor size and prolonged animal survival in the orthotopic brain models (EML4-ALK and EML4-ALK^{L1196M}) in mice. The anti-tumor efficacy of lorlatinib was dose dependent and demonstrated strong correlations to inhibition of ALK or ROS1 phosphorylation. The plasma levels associated with the anti-tumor efficacy in EML4-ALK^{L1196M} dependent human NSCLC cell line models were utilized to project target human plasma concentrations for clinical studies.

Among the 53 patients who were evaluable for efficacy in the Phase 1 part of the study as of the data cutoff date, the ORR was 47.2% and included 3 (5.75%) confirmed complete responses (CRs), and 22 (41.5%) confirmed partial responses (PRs). Ten (10) patients (18.9%) had stable disease (SD) as their best overall response.

Thirty-nine (72%) Phase 1 patients had CNS metastases at study entry. Of the 39 patients evaluable for intracranial response at the time of the data cutoff, 10 (25.6%) patients had a confirmed CR and 4 (10.3%) patients had a confirmed PR, resulting in an intracranial ORR of 35.9%. Further, 13 (33.3%) patients had SD as their best overall response.

The clinical safety data available to date with single-agent lorlatinib in patients with advanced NSCLC who received ≥1 previous treatment(s) have suggested an acceptable safety profile of the compound. Most of the observed events were in line with the underlying disease. Anti-tumor activity with lorlatinib observed on both extracranial and intracranial lesions, has showed good BBB (blood brain barrier) penetration associated with clinically significant activity on brain metastases. The resulting potential for CNS toxicity some of which were predicted using preclinical models, has been monitored in the clinic by studying the effect of different administration schedules (BID vs QD) and with the use of formal neurological assessment to better characterize the changes seen. The selected administration schedules for Phase 2 and 3 study of 100 mg QD has been associated with reduction of CNS toxicity.

Hypertriglyceridemia and hypercholesterolemia have been identified as risks associated with the administration of lorlatinib. Respective safety risk mitigation measures have been implemented in the ongoing studies and are also included in this clinical trial protocol. These include instructions for proper management of hyperlipidemia and a list of recommended statins (see Section 5.5.1.1). Close safety monitoring will be performed throughout the study as outlined in the Schedule of Activities table.

Peripheral neuropathy, Mood Disorders, Cognitive Disorders, Speech Disorders, Vision Disorders, Diarrhoea, Constipation, Arthralgia, Oedema, Fatigue, Weight Increased are others identified risks associated with lorlatinib administration, for which dose delay/dose reduction has been effective.

For complete details of the in vitro /nonclinical/clinical studies, refer to lorlatinib current investigator's brochure.

Crizotinib is approved multinationally as the SOC for the treatment of ALK-positive NSCLC, both treatment-naïve or after failure of prior systemic therapy. Overall, the adverse events reported for crizotinib in clinical studies are considered tolerable and manageable, and the safety profile of crizotinib is well characterized and described in the XALKORI package insert.

Overall, the anticipated benefit-risk profile supports the investigation of lorlatinib head-to-head against the SOC crizotinib in the patient population chosen for this study.

CCI [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective:	Primary Endpoint:
• To demonstrate that lorlatinib as a single agent (Arm A) is superior to crizotinib alone (Arm B) in prolonging Progression-Free Survival (PFS) in advanced ALK-positive NSCLC patients who are treatment naïve.	• PFS based on blinded independent central review (BICR) assessment (RECIST v.1.1).
Secondary Objectives:	**Secondary Endpoints:**
• To compare Arm A and Arm B in treatment-naïve advanced ALK-positive NSCLC patients with respect to Overall Survival (OS); • To evaluate the antitumor activity in each treatment arm; • To evaluate the safety and tolerability in each treatment arm; • To evaluate patient-reported outcomes (PROs) of health-related quality of life, disease/treatment-related symptoms of lung cancer, and general health status for each treatment arm; • To evaluate candidate biomarkers of sensitivity or resistance to single-agent crizotinib or lorlatinib in pre-treatment tumor tissue; • To evaluate candidate biomarkers of sensitivity or resistance to single-agent crizotinib or lorlatinib in peripheral blood.	• Efficacy: OS, PFS based on Investigator's assessment, OR based on BICR and on Investigator's assessment; intracranial OR (IC-OR), IC-TTP, DR and IC-DR, TTR and IC-TTR all by BICR (RECIST v. 1.1) and PFS2; • Safety: AEs (as graded by NCI CTCAE v.4.03); laboratory abnormalities (as graded by NCI CTCAE v.4.03); vital signs (blood pressure, pulse rate) and body weight; electrocardiograms (ECGs); echocardiogram or MUGA scan; ophthalmologic data; • PROs as assessed by EORTC QLC-C30, EORTC QLQ-LC13, EQ-5D-5L; • Tumor tissue biomarkers including, but not limited to, ALK gene rearrangement and/or mutation as measured by next-generation sequencing (NGS) and/or immunohistochemistry (IHC); • Peripheral blood cfDNA (circulating free Deoxyribonucleic acid) biomarkers including, but not limited to, ALK gene rearrangement and/or ALK kinase domain mutations.

Exploratory Objectives:	Exploratory Endpoints:
[redacted]	[redacted]

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

3. STUDY DESIGN

This is a Phase 3, multinational, multicenter (at approximately 160 sites) , randomized, open-label, parallel 2-arm study in which approximately 280 patients with previously untreated advanced ALK-positive NSCLC were to be randomized 1:1 to receive lorlatinib monotherapy or crizotinib monotherapy according to the study design shown in Figure 1 (296 patients were actually randomized).

Patients will be stratified according to (also see Section 5.1.1):

- Presence of brain metastases (Yes vs No);
- Ethnic origin (Asian vs Non-Asian).

Crossover between treatment arms will not be permitted.

3.1. Study Treatment

This study was to randomize approximately 280 patients in a 1:1 ratio to receive:

- Arm A: Lorlatinib single agent;
- Arm B: Crizotinib single agent.

A cycle duration will be 4 weeks (28 days) and will always be considered 4 weeks irrespective of any dose delays/dosing interruptions or missed doses which may affect nominal days of each cycle.

Study treatment may continue until confirmed disease progression assessed by BICR, patient refusal, patient lost to follow-up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.4 Patient Withdrawal).

Patients who develop radiological disease progression confirmed by BICR assessment but are otherwise continuing to derive clinical benefit from study treatment will be eligible to continue with the treatment they have been assigned to, provided that the treating physician has determined that the benefit/risk for doing so is favorable. See Section 7.2 for details on expedited BICR assessment of disease progression.

Details of the study treatment forms and packaging and recommendations for dose modifications are included in the Study Treatment Section 5 of the protocol.

4. SUBJECT ELIGIBILITY CRITERIA

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom participation in the study is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether a particular patient is suitable for this protocol.

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

4.1. Inclusion Criteria

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

1. Diagnosis:

   a. Study Population: Patients with histologically or cytologically confirmed diagnosis of locally advanced [(Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) by American Joint Committee on Cancer (AJCC) v 7.0] ALK-positive NSCLC where ALK status is determined by the FDA-approved (for use in US), CE (Conformité Européene) marked (for EU and other countries that accept CE marking), and PMDA(Pharmaceuticals and Medical Devices Agency)-approved (for use in Japan) Ventana ALK (D5F3) Companion Diagnostic (CDx) IHC test performed on the Ventana ULTRA or XT platforms (refer to Section 6.1.1.1 for any prescreening activity related to ALK determination);

   b. Tumor Requirements: At least 1 extracranial measurable target lesion per RECIST v. 1.1 that has not been previously irradiated. CNS metastases are allowed if **asymptomatic** and:

      1. Either untreated and not currently requiring corticosteroid treatment, or on a stable or decreasing dose of ≤10 mg QD prednisone or equivalent; or

2. Local treatment has been completed with full recovery from the acute effects of radiation therapy or surgery prior to randomization, and if corticosteroid treatment for these metastases has been withdrawn for at least 4 weeks with neurological stability; or

3. In case of leptomeningeal disease (LMD) or carcinomatous meningitis (CM) if visualized on magnetic resonance imaging (MRI), or if baseline CSF positive cytology is available.

c. Tissue Requirements: All patients must have an archival formalin fixed, paraffin embedded (FFPE) tissue specimen available and collected prior to randomization. If archived tissue is unavailable, then a mandatory *de novo* biopsy must be performed.

2. No prior systemic NSCLC treatment for advanced (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) disease, including molecularly targeted agents (eg, ALK TKIs), angiogenesis inhibitors, immunotherapy, or chemotherapy. Prior treatment for earlier Stages of the NSCLC only allowed if completed more than 12 months prior to randomization.

3. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0, 1, or 2.

4. Age ≥18 years (or ≥20 years as required by local regulation).

5. Adequate Bone Marrow Function, including:

a. Absolute Neutrophil Count (ANC) ≥ 1,500/mm^3 or ≥1.5 x 10^9/L;

b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;

c. Hemoglobin ≥9 g/dL.

6. Adequate Pancreatic Function, including:

a. Serum total amylase ≤1.5 x upper limit of normal (ULN)*;

b. Serum lipase ≤1.5 x ULN.

*if total amylase >1.5 x ULN, but pancreatic amylase is within the ULN, then patient may be enrolled.

7. Adequate Renal Function, including:

a. Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥60 mL/min as calculated using the method standard for the institution.

8. Adequate Liver Function, including:

a. Total serum bilirubin ≤1.5 x ULN;

b. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) ≤2.5 x ULN (≤5.0 x ULN in case of liver metastases).

9. Acute effects of prior radiotherapy resolved to baseline severity or to CTCAE Grade ≤1 except for AEs that in the investigator's judgment do not constitute a safety risk for the patient.

10. Serum pregnancy test (for females of childbearing potential) negative at screening. Female patients of non-childbearing potential must meet at least 1 of the following criteria:

- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause (which may be confirmed with a serum follicle-stimulating hormone [FSH] level confirming the postmenopausal state if appropriate);
- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure.

All other female patients (including female patients with tubal ligations) are considered to be of childbearing potential.

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

12. Willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures.

4.2. Exclusion Criteria

Patients with any of the following characteristics/conditions will not be included in the study:

1. Spinal cord compression unless the patient has good pain control attained through therapy, and there is stabilization or recovery of neurological function for the 4 weeks prior to randomization.

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

3. Radiation therapy within 2 weeks prior to randomization, including stereotactic or partial brain irradiation. Patients who complete whole brain irradiation within 4 weeks prior to randomization or palliative radiation therapy outside of the CNS within 48 hours prior to randomization will also not be included in the study.

4. 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.

5. Known prior or suspected severe hypersensitivity to study drugs or any component in their formulations.

6. Active and clinically significant bacterial, fungal, or viral infection including hepatitis B virus (HBV) or hepatitis C virus (HCV) (eg, in case of known HBsAg or HCV antibody positivity), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness.

7. 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:

   - Arterial disease such as cerebral vascular accident/stroke (including Transient Ischemic Attack -TIA), myocardial infarction, unstable angina;

   - Venous diseases such as cerebral venous thrombosis, symptomatic pulmonary embolism;

   - Non-vascular cardiac disease such as congestive heart failure (New York Heart Association Classification Class ≥ II), second-degree or third-degree AV block (unless paced) or any AV block with PR >220 msec; or ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 bpm (unless patient is otherwise healthy such as long-distance runners, etc.), machine-read Electrocardiogram (ECG) with QTc >470 msec, or congenital long QT syndrome.

8. Patients with predisposing characteristics for acute pancreatitis according to investigator judgment (eg, uncontrolled hyperglycemia, current gallstone disease) in the last month prior to randomization.

9. History of extensive, disseminated, bilateral or presence of Grade 3 or 4 interstitial fibrosis or interstitial lung disease including a history of pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, and pulmonary fibrosis.

10. Evidence of active malignancy (other than NSCLC, non-melanoma skin cancer, or localized prostate cancer or any in situ cancer which does not currently require treatment) within the last 3 years prior to randomization.

11. 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 or crizotinib.

    a. Known strong CYP3A inhibitors (eg, strong CYP3A inhibitors: grapefruit juice or grapefruit/grapefruit related citrus fruits [eg, Seville oranges, pomelos], boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, 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. The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

    b. 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 US market).

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

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

12. 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 patient inappropriate for entry into this study.

13. Patients who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or patients who are Pfizer employees, including their family members, directly involved in the conduct of the study.

14. Participation in other studies involving investigational drug(s) within 2 weeks prior to study entry and/or during study participation.

15. Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 97 days, if male or 35 days if female, after the last dose of investigational product if under lorlatinib or 90 days if under crizotinib.

4.3. Lifestyle Requirements

4.3.1. Contraception

Lorlatinib is teratogenic and an aneugen and can therefore cause harm when administered to a pregnant woman. Crizotinib can also cause fetal harm when administered to a pregnant woman. Therefore, use of an appropriate method of contraception during treatment with these study drugs is mandatory.

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected a highly effective method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see below, Section 4.3.1.2) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities (SoA), the investigator or designee will inform the participant of the need to use a highly effective method of contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least one of the appropriate methods of contraception listed below, Section 4.3.1.2).

Patients receiving lorlatinib:

Women of childbearing potential (WOCBP, definition provided below, Section 4.3.1.1) must agree to use a highly effective nonhormonal method of contraception, because lorlatinib can render hormonal contraceptives ineffective. If a hormonal method of contraception is unavoidable, then a condom must be used in combination with the hormonal method. Contraception must be continued for at least 35 days after completing therapy.

During treatment with lorlatinib and for at least 97 days after the final dose, male patients with WOCBP partners must agree to use a highly effective method of contraception, including a condom, and male patients with pregnant partners must be agreed to use condoms (see Section 4.3.1.2).

Patients receiving crizotinib:

WOCBP and male patients with WOCBP partners must agree to use an highly effective method of contraception (see Section 4.3.1.2) throughout the study and continue to do so for at least 90 days after last dose of crizotinib.

Patients receiving either lorlatinib or crizotinib:

All sexually active male patients must agree to prevent potential transfer to and exposure of pregnant partner(s) and fetus to drug through ejaculate by using a condom consistently and correctly, beginning with the first dose of lorlatinib or crizotinib and continuing for at least 97 days after the last dose of lorlatinib, or 90 days after the last dose of crizotinib.

In addition, the investigator or designee will instruct the patient to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

4.3.1.1. Woman of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

1. 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 categories 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.

2. Postmenopausal female:

   A postmenopausal state is defined as age 60 years 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 hormone replacement therapy (HRT).
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal appropriate 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.

4.3.1.2. Methods of Contraception

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided a condom is used in combination with the hormonal method. The patient must have been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

4. Male condom must be used in association with a female highly effective method of contraception.

5. Male sterilization with absence of sperm in the postvasectomy ejaculate.

NOTE: For subjects not sexually active, sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (during the entire period of risk associated with the study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject. Investigator should assess at each visit if a change of patient lifestyle occurred and in case reconsider, in consultation with the patient, to select an appropriate method of contraception for the individual patient and his/her partner(s) from the list of permitted contraception methods.

4.4. 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 study manual.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, patients are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, patient 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 patient'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. The contact number is not intended for use by the patient directly, and if a patient calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Conference on Harmonisation (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference/comparator in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33).

For this study, the investigational products are lorlatinib (PF-06463922) and crizotinib (Xalkori), which is the reference comparator.

5.1. Allocation to Treatment

The investigator's knowledge of the treatment should not influence the decision to enroll a particular patient or affect the order in which patients are enrolled.

A patient must sign an informed consent form (ICF) before being evaluated for study entry. Once a patient who has met inclusion and exclusion criteria has provided a signed ICF, allocation of patients to the treatment arms will proceed through the use of an interactive response technology (IRT) system (interactive web-based response [IWR]). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's identification (ID) and password, the protocol number, and the patient number. The site personnel will then be provided with a treatment assignment, randomization number, and dispensable unit (DU) or container number when investigational product is being supplied via the IRT system. The IRT system will provide a confirmation report containing the subject number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

Note: The IRT is the source of the patient number. The IRT system will provide the patient number at the end of the first IRT patient transaction. Study treatment must be initiated preferably on the randomization day but no later than 7 days after randomization.

Qualified patients will be randomized in a 1:1 ratio to receive:

- Arm A: Lorlatinib monotherapy at the RP2D of 100 mg QD, administered as 4 x 25 mg oral tablets, continuously.

- Arm B: Crizotinib monotherapy at the registered starting dose of 250 mg BID, administered as 1 x 250 oral capsules/twice daily, continuously.

5.1.1. Stratification Factors

Allocation of patients will be stratified according to:

- Presence of brain metastases.

- Yes* vs No.

* Yes: means that the brain lesions can be either present and observed at patient entry or known from the patient medical history to have been present in the past even if no longer visible (eg, irradiated or surgically removed lesions, etc). The brain lesions can be either measurable or non- measurable lesions, and can be classified as either target or non-target lesions.

- Ethnic origin**
  - Asian vs non-Asian.

**This refers to the actual patient race, not the place where he/she lives or is treated. If the patient's parents are 50% Asian and 50% non-Asian, the patient must be treated as non-Asian; in case 75% Asian and 25% non-Asian, patient is treated as Asian; in case 75% non-Asian and 25% Asian patient is treated as non-Asian.

This stratified randomization will be centrally allocated across all centers via the IRT system. A central randomization will be adopted due to the high number of participating centers in contrast to the anticipated small number of patients randomized at each center.

5.2. Patient Compliance

For self-administration of lorlatinib or crizotinib at home, compliance will be captured and completed by the patient.

A patient diary will be provided to the patients to aid in lorlatinib (Arm A) and crizotinib (Arm B) compliance. The diary will be maintained by the patient to include unchanged, missed, or changed lorlatinib (Arm A) or crizotinib doses (Arm B).

In Arm A, patients will be required to return to the investigational site all bottles of lorlatinib at the end of each 28-day cycle during the planned visit at the site. The number of lorlatinib tablets remaining will be documented and recorded at each clinic visit.

In Arm B, patients will be required to return to the investigational site all bottles of crizotinib at the end of each 28-day cycle during the planned visit at the site. The number of crizotinib capsules remaining will be documented and recorded at each clinic visit.

The study site must follow up (for example, via a telephone call) with each patient on Cycle 1 Day 5 (±3 days) to confirm that the patient understands and is in compliance with lorlatinib or crizotinib dosing instructions. If needed, the patient will be re-trained. The same follow- up process will be applied in case the dose of lorlatinib or crizotinib is modified during the treatment period.

5.3. Investigational Product Supplies

Lorlatinib and crizotinib will be supplied for the study by Pfizer Global Clinical Supply.

Drug supplies will be shipped to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed and filed, as directed on the bottom of the Drug Shipment

and Proof of Receipt form. The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

5.3.1. Dosage Forms and Packaging

5.3.1.1. Lorlatinib (PF-06463922)

Lorlatinib will be supplied for oral administration as 25 mg tablets in High-Density Polyethylene (HDPE) bottles with desiccant and labeled according to local regulatory requirements.

5.3.1.2. Crizotinib

Crizotinib will be supplied for oral administration as capsules containing 200 mg or 250 mg of investigational product and will be packaged in -High-Density Polyethylene (HDPE) bottles and labeled according to local regulatory requirements.

5.3.2. Preparation and Dispensing

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of investigational agents. Investigational product should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance.

5.3.2.1. Lorlatinib (PF-06463922)

Lorlatinib will be dispensed at the beginning of every 28-day cycle (or as otherwise indicated) using an IRT drug management system. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Lorlatinib will be provided in bottles containing 25 mg tablets. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given sufficient supply to last until their next study visit. Patients will be provided with Drug Administration Cards and Patient Diaries. In addition, administration instructions will be detailed for site personnel in the Investigational Product (IP) Manual.

5.3.2.2. Crizotinib

Crizotinib will be dispensed at the beginning of every 28-day cycle (or as otherwise indicated) using an IRT drug management system. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Crizotinib will be provided in bottles containing 200 mg or 250 mg capsules. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given sufficient supply to last until their next study visit. Patients will be provided with Drug Administration Cards and Patient Diaries. In addition, administration instructions will be detailed for site personnel in the IP Manual.

5.4. Administration

All trial treatments will be administered on an outpatient basis.

A cycle is defined as 28 days, irrespective of any dose delays/dosing interruptions or missed doses which may affect nominal days of each cycle.

5.4.1. Lorlatinib (PF-06463922)

Lorlatinib will be administered orally QD at approximately the same time of the day on a continuous daily dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity. Patients must swallow the study medication whole and must not manipulate or chew the medication prior to swallowing. A dosing card will be provided to the patients to provide guidance for the correct use of lorlatinib. Patients must be instructed that should they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose. Instead, resume the subsequent doses as originally prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. The patient must be instructed to record all doses (including missed or vomited) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and Case Record Forms (CRFs).

CCI [redacted] On ECG assessment days, the lorlatinib dose should be taken in the clinic under the supervision of the study site personnel so that timing of assessments is appropriately synchronized.

Since no clinically meaningful effect of food on the PK of lorlatinib has been observed, lorlatinib can be administered with or without food.

5.4.2. Crizotinib

Crizotinib will be administered orally BID at approximately the same time in the morning and evening 12 hours apart on a continuous daily dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity. Patients must swallow the study medication whole and must not manipulate or chew the medication prior to swallowing.

A dosing card will be provided to the patients to provide guidance for the correct use of crizotinib. Patients must be instructed that should they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose. Instead, resume the subsequent doses as originally prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. If a patient inadvertently takes 1 extra dose during a day, the patient should not take the next dose. The patient must be instructed to record all doses (including missed or vomited) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

On ECG triplicate assessment day, the crizotinib doses should be taken in the clinic under the supervision of the study site personnel so timing of assessments is appropriately synchronized.

Oral crizotinib will be administered with at least 8 oz (240 mL) of water with or without food.

5.4.3. Treatment Duration

Treatment will continue until confirmation of disease progression, patient refusal, or unacceptable toxicity, whichever occurs first. Once the patient has documented PD by BICR, patients should be discontinued from study treatment.

However, if according to the Investigator's clinical judgment, a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with the assigned study drug after discussion between the Investigator and Pfizer. The Investigator's judgment should be based on the overall benefit/risk assessment (eg, intracranial response), and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data. In that case, the patient must undergo the same assessments foreseen during the active treatment period. As far as tumor assessments:

- If only extracranial progression was documented, with intracranial lesions stable or in response, intracranial assessments should be performed until intracranial PD;
- Once intracranial PD is documented no further tumor assessments are required.

At completion of the study (ie, after the required number of OS events have been reported), drug supply for patients benefiting from therapy may continue beyond closure of the study without further data collection. At that time, patients not progressed or still experiencing clinical benefit may be candidates for continued treatment, provided that the treating physician has determined that the benefit/risk assessment for continuing study treatment is favourable. A number of options will be considered for patients to continue to receive the study drug outside of the trial without any financial obligation to the patient. These options may include, but are not be limited to, locally reimbursed commercial drug, or donated drug or other options available at that time. A local country Pfizer representative will work with the Investigator to determine which will be the best option for each individual patient.

5.5. Recommended Dose Modifications

Every effort should be made to administer investigational products on the planned dose and schedule. In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify their investigators at the first occurrence of any adverse event.

If a dosing interruption longer than 6 weeks due to ongoing treatment-related toxicity is necessary, study treatment should be permanently discontinued, unless there is a discussion of the clinical circumstance with the sponsor's medical monitor and agreement that the patient may resume treatment after a lapse of greater than 6 weeks.

Dose levels for lorlatinib and crizotinib dose modifications are provided in Section 5.5.1 and Section 5.5.2. All dose modifications will be reported in the Case Report Form (CRF).

5.5.1. Lorlatinib Dose Modifications

In case of adverse events, Investigators are encouraged to employ best supportive care according to local institutional clinical practices or follow the guidance for selected adverse events provided in Table 2.

Patients will be monitored closely for toxicity, and the dose of lorlatinib may be adjusted as indicated in Table 1 below.

Table 1. Lorlatinib Dose Levels for Intra-patient Dose Modifications

Dose Levels	Lorlatinib Dose
0	100 mg QD
-1	75 mg QD
-2	50 mg QD
Dose reductions below dose level -2 are not allowed.	

Intra-patient dose reduction by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered (Dose Level -1 is 75 mg QD; Dose Level -2 is 50 mg QD).*

If a patient has a significant toxicity from lorlatinib treatment which fails to recover within 42 days (6 weeks) or, in the opinion of the investigator, requires permanent discontinuation of the treatment based on the severity of the adverse event, then this patient should not be further treated with lorlatinib but should remain in the trial with ongoing tumor assessments until RECIST-defined disease progression by the BICR.

Recommendations for lorlatinib dose modification for treatment-related non-hematological and hematological toxicity, as well as for treatment-related toxicity of special interest, are provided in Table 2 below.

Re-escalation is not allowed except if discussed with and approved by the sponsor's medical contact.

*it is recommended that in case of lorlatinib dose decrease, the patient is assigned new drug rather than using less tablets from the bottle assigned at previous visit.

Table 2. Arm A Patients: Lorlatinib Dose Modifications for Lorlatinib-Related Toxicities

Non-Hematologic Toxicities

Toxicity	Grade 1**	Grade 2**	Grade 3	Grade 4
Pancreatitis	NA	If elevated enzymes (both amylase and lipase are Grade ≤2) are observed in the absence of radiological findings of pancreatitis: continue lorlatinib at the same dose level without dose hold. Repeat lipase and amylase and obtain pancreatic isoenzyme if possible. If radiologically confirmed pancreatitis: withhold lorlatinib dose. Repeat radiology and lipase and amylase weekly and obtain pancreatic isoenzyme. If appropriate, resume lorlatinib treatment at one dose level lower if radiology has returned to baseline and lipase and amylase are Grade ≤2.	Permanently discontinue lorlatinib.	Permanently discontinue lorlatinib.
Pneumonitis (in the absence of disease progression, pulmonary embolism, positive cultures or radiation effect)§.	Asymptomatic, radiographic findings only: No need for lorlatinib dose adjustment. Initiate appropriate monitoring.	Withhold current lorlatinib dose until toxicity has returned to baseline. Rule out infection and consider initiating treatment with corticosteroids. Then resume lorlatinib treatment at one dose level lower. Discontinue lorlatinib permanently if pneumonitis recurs or if failure to recover after 6 weeks of study treatment hold and steroid treatment.	Permanently discontinue lorlatinib.	Permanently discontinue lorlatinib.
Electrocardiogram QTc prolongation (see Section 5.5.1.2).	Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Continue lorlatinib at the same dose level.	Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Continue lorlatinib at the same dose level.	Withhold lorlatinib dose. Assess electrolytes and concomitant medications. Correct any electrolyte abnormalities, or hypoxia. Upon recovery to Grade ≤1 resume lorlatinib treatment at one dose level lower.	Permanently discontinue lorlatinib.
LV Dysfunction	CTCAE v4.03 does not report Grade 1.	CTCAE v 4.03 does not report Grade 2.	Permanently discontinue lorlatinib.	Permanently discontinue lorlatinib.
Non-Hematologic General	Continue lorlatinib at the same dose level.	Continue lorlatinib at the same dose level.	Withhold lorlatinib dose until toxicity is Grade ≤1(or has returned to baseline) then reduce the dose by 1 level or rechallenge at the same dose.*	Withhold dose until toxicity is Grade ≤1 (or has returned to baseline), then reduce the dose by 1 level* or

				discontinue at the discretion of the investigator.

* Patients who develop asymptomatic Grade 4 hyperuricemia or Grade 3 hypophosphatemia may continue lorlatinib without dose modification at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy to require lorlatinib dose modification (for more detailed guidelines, see Section 5.5.2.1 and 5.5.2.2).

** In cases where no specific dose adjustments for Grade 1 or Grade 2 treatment-related toxicity are provided, investigators should always manage their patients according to their medical judgment which may include dose reduction or interruption based on the particular clinical circumstances.

§ If a patient has a potential diagnosis of pneumonitis or drug-related lung injury the same evaluations/procedures provided in Section 5.5.2.4 should be considered to assist or exclude the diagnosis of pneumonitis during this period.

Hematologic Toxicities				
Toxicity	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hematologic General	Continue lorlatinib at the same dose level.	Continue lorlatinib at the same dose level.	Withhold lorlatinib dose until toxicity is Grade ≤1 (or has returned to baseline), then rechallenge at the same dose or reduce the dose by 1 dose level.	Withhold lorlatinib dose until toxicity is Grade ≤1 (or has returned to baseline) then rechallenge at the same dose or reduce the dose by 1 dose level.
Lymphopenia	Continue lorlatinib at the same dose level.	Continue lorlatinib at the same dose level.	If no evidence of infection or other clinically significant toxicity, continue lorlatinib at the same dose; otherwise, withhold dose until toxicity is Grade ≤1 (or baseline) then rechallenge at the same dose or reduce by 1 level.	If no evidence of infection or other clinically significant toxicity, continue lorlatinib at same dose; otherwise, withhold dose until toxicity is Grade ≤1 (or baseline), then rechallenge at the same dose or reduce the dose by 1 dose level.
Lipid Elevation Toxicities[α]				
Cholesterol	Continue lorlatinib at the same dose. Consider introducing use of a statin or other lipid lowering agent as	Introduce the use of a statin or other lipid lowering agent as appropriate, and continue lorlatinib at the same dose.	Introduce the use of a statin or other lipid-lowering agent as appropriate, or increase the dose of the statin/lipid lowering agent	Increase the dose of the statin or other lipid-lowering agents, or change to a new statin/lipid lowering agent. Withhold lorlatinib dose until toxicity is

	appropriate based on investigator's medical judgment.		or change to a new agent. Either continue lorlatinib at the same dose without interruption or withhold dose until toxicity is Grade ≤2 and then continue at the same dose.	Grade ≤2 and then reduce the dose by 1 dose level or rechallenge at the same dose.
Triglycerides	Continue lorlatinib at the same dose. Consider introducing use of a statin or other lipid-lowering agent as appropriate based on investigator's medical judgment.	Introduce the use of a statin or other lipid-lowering agent as appropriate, and continue lorlatinib at the same dose.	Introduce the use of a statin or other lipid-lowering agent as appropriate, or increase the dose of the statin/lipid-lowering agent or change to a new agent. Either continue lorlatinib at the same dose without interruption or withhold dose until toxicity is Grade ≤2 and then continue at the same dose.	Increase the dose of the statin or other lipid-lowering agents, or change to a new statin/lipid-lowering agents. Withhold lorlatinib dose until toxicity is Grade ≤2 and then reduce the dose by 1 dose level or rechallenge at the same dose.
[α] See also instructions provided in Section 5.5.1.1 Hyperlipidemia.				

CNS Toxicities				
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
CNS effects[β]	Continue lorlatinib at the same dose or withhold dose until recovery to baseline.	Continue lorlatinib at same dose or withhold dose until recovery to Grade ≤1. Consider dose reduction or rechallenge at the same dose.	Withhold lorlatinib dose until toxicity is Grade ≤1. Reduce dose to the next lower dose.	Permanently discontinue lorlatinib.

[β] Examples of CNS effects could include changes in speech, memory, sleep, cognition, or vision.

5.5.1.1. Hyperlipidemia

In the lorlatinib Phase 1 Study B7461001, hypercholesterolemia was the most common AE reported. Elevations in lipids usually begin in the first few cycles and, if statins are not introduced, can rise to Grade 3 levels by the next treatment cycle. Therefore, the suggested management is to begin a statin for Grade 1 elevations in either cholesterol or triglycerides and to increase the statin dose if adequate control is not obtained, as outlined in Table 2.

Members of the statin class of agents are differentially sensitive to CYP3A4, and **caution should be exercised when selecting statin for management of elevated lipid levels.**

Pitavastatin and rosuvastatin can be used during lorlatinib treatment without dose adjustment since there is no CYP3A4 involvement in their elimination. Pravastatin, fluvastatin and atorvastatin should be used with caution during lorlatinib treatment, and a dose adjustment of these statins may be necessary **(increasing dose may be considered)**. Lovastatin and simvastatin are not recommended for use during lorlatinib treatment.

5.5.1.2. PR Interval Prolongation

Analysis of ECG data from ongoing and completed human studies with lorlatinib has identified a subset of patients who exhibited ECG evidence of PR interval prolongation. The ECG changes appear limited to the PR interval with no impact on QRS or QT intervals. This impact on the PR interval is supported by preclinical animal studies as described in the current lorlatinib IB.

Guidance for management of PR interval prolongation is provided in Table 3 below and examples of drug with potential PR interval prolongation effect can be found in Appendix 5.

Table 3. PR Interval Prolongation Management

Toxicity	Not Symptomatic	Symptomatic
1st-Degree Heart Block (PR interval >200 msec)	**No dose hold or reduction needed.** Assess concomitant medications. Monitor closely by obtaining pre-dose ECG at next visit, even if unscheduled. Instruct patient to call if symptoms develop that may be related to heart block.	**Withhold dose.** Assess concomitant medications. Obtain ECG in approximately 48 hours and re-assess symptoms and PR-interval. Restart at same dose or consider dose reduction when symptoms resolve.
2nd-Degree Heart Block	**Withhold dose.** Assess concomitant medications. Repeat ECG in approximately 48 hours. Instruct patient to call if symptoms develop that may be related to heart block. Restart at same dose or consider dose reduction if subsequent ECG does not show 2nd degree block.	**Withhold dose.** Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic heart block persists. Resume at reduced dose only when symptoms resolve AND 2nd degree block resolves. If patients revert to 1st degree block with no symptoms, resume at reduced dose.
Complete Heart Block	**Withhold dose.** Refer for cardiac observation and monitoring. Temporary pacemaker placement may be indicated for severe symptoms associated with heart block. If heart block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, may resume at full dose. If no pacemaker placed, permanently discontinue lorlatinib.	

5.5.2. Crizotinib Dose Modifications

In case of adverse events, Investigators are encouraged to employ best supportive care according to local institutional clinical practices and follow the guidance for selected adverse events provided below.

Patients will be monitored closely for toxicity, and the dose of crizotinib may be adjusted as indicated in Table 4 below.

Table 4. Crizotinib Dose Levels for Intra-patient Dose Modifications

Dose Levels	Crizotinib Dose
0	250 mg BID
-1	200 mg BID
-2	250 mg QD
Dose reductions below dose level -2 level are not allowed.	

Intra-patient dose reduction by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered (Dose Level -1 is 200 mg BID; Dose Level -2 is 250 mg QD). Treatment continuation for patients requiring more than 2 dose reductions due to treatment-related toxicity is not allowed.

If a patient has a significant toxicity from crizotinib treatment which fails to recover within 42 days (6 weeks) or, in the opinion of the investigator, requires permanent discontinuation of the treatment based on the severity of the adverse event, then this patient should not be further treated with crizotinib but should remain in the trial with ongoing tumor assessments until RECIST-defined disease progression by the BICR.

Recommendations for crizotinib dose modifications for treatment-related toxicities are provided in Table 5 below.

Re-escalation is not allowed except for the cases specified in Table 5.

Table 5. Arm B Patients: Crizotinib Dose Modifications for Crizotinib-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
ALT elevation possibly related to crizotinib with total bilirubin <2 X ULN.	Continue crizotinib at the same dose level.	Continue crizotinib at the same dose level. Obtain repeat ALT and total bilirubin when symptomatic or within 7 days. §Country-specific guidelines may also apply.	Withhold crizotinib dose until toxicity is Grade ≤1, or has returned to baseline, then resume treatment by reducing by one dose level. If Grade 3 ALT elevation recurs reduce further (at most by 2 dose levels from the initial dose level). If recurrence at dose level -2, then discuss with sponsor whether or not to discontinue permanently. If ALT elevation does not recur after at least 4 weeks, the dose may be escalated by single dose level increments up to the initial dose level. §Country-specific guidelines may also apply.	See Grade 3 §Country-specific guidelines may also apply.
ALT elevation and total bilirubin elevation ≥2X ULN (in absence of cholestasis or hemolysis).	Continue crizotinib at the same dose level. Obtain repeat ALT and total bilirubin within 48 hours.	Discontinue crizotinib treatment and do not retreat.	Discontinue crizotinib treatment and do not retreat.	Discontinue crizotinib treatment and do not retreat.

Table 5. Arm B Patients: Crizotinib Dose Modifications for Crizotinib-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Bradycardia (heart rate less than 60 beats per minute). See also instructions in Section 5.5.2.3.	Continue crizotinib at the same dose level.	Withhold crizotinib until recovery to Grade ≤1 or to heart rate ≥60. Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume crizotinib at previous dose upon recovery to Grade ≤1 or to heart rate ≥60. If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume crizotinib at reduced dose upon recovery to Grade ≤1 or to heart rate ≥60.	Same as for Grade 2 bradycardia.	Permanently discontinue crizotinib if no contributing concomitant medication is identified. If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume crizotinib at 250 mg once daily upon recovery to Grade ≤1 or to heart rate ≥60, with frequent monitoring Permanently discontinue crizotinib for recurrence.

Table 5. Arm B Patients: Crizotinib Dose Modifications for Crizotinib-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis (not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect). See also instructions in Section 5.5.2.4.	Discontinue crizotinib treatment and do not retreat.	Discontinue crizotinib treatment and do not retreat.	Discontinue crizotinib treatment and do not retreat.	Discontinue crizotinib treatment and do not retreat.
Left ventricular systolic dysfunction.	Continue crizotinib at the same dose level.	Continue crizotinib at the same dose level.	Discontinue crizotinib treatment and do not retreat.	Discontinue crizotinib treatment and do not retreat.
Electrocardiogram QTc prolongation.	Continue crizotinib at the same dose level.	Assess electrolytes and concomitant medications Correct any electrolyte or magnesium abnormalities Continue crizotinib at the same dose level.	Interrupt crizotinib until recovery to Grade ≤1. Assess and correct electrolytes and concomitant medications. Upon recovery to Grade ≤1, resume crizotinib treatment by reducing the dose by one dose level if no other cause for QTc prolongation is found otherwise resume crizotinib at the same dose level.	Discontinue crizotinib treatment and do not retreat.
Vision disorders‡	Continue crizotinib at the same dose level Repeat ophthalmologic consultation.	Continue crizotinib at the same dose level Repeat ophthalmologic consultation.	Interrupt crizotinib until recovery to Grade ≤1. Repeat ophthalmologic consultation‡ Resume crizotinib treatment by reducing the dose by one dose level upon recovery to Grade ≤1.	Discontinue crizotinib and do not retreat. Repeat ophthalmologic consultation.
Non-Hematologic General (excluding those mentioned above).	Continue crizotinib at the same dose level.	Continue crizotinib at the same dose level.	Withhold crizotinib dose until toxicity is grade ≤1, or has returned to baseline, then resume crizotinib treatment at the same dose or reduce the dose by 1 level at the discretion of the investigator.*	Withhold crizotinib dose until toxicity is grade ≤1, or has returned to baseline, then reduce crizotinib dose by 1 level and resume treatment, or discontinue at the discretion of the investigator.*

Table 5. Arm B Patients: Crizotinib Dose Modifications for Crizotinib-Related Toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic (excluding lymphopenia†).	Continue crizotinib at the same dose level.	Continue crizotinib at the same dose level.	Withhold crizotinib dose until toxicity is grade ≤2, or has returned to baseline, then resume crizotinib treatment at the same dose level or reduce the dose by 1 dose level after discussion with the sponsor.†	Withhold crizotinib dose until toxicity is grade ≤2, or has returned to baseline, then reduce the crizotinib dose by 1 level and resume treatment†

*Patients who develop Grade 4 hyperuricemia or Grade 3 hypophosphatemia without clinical symptoms may continue study treatment without interruption at the discretion of the investigator. Nausea, vomiting or diarrhea must persist at Grade 3 or 4 despite maximal medical therapy, to require dose modification.

†Patients who develop Grade 3 or 4 lymphopenia without other dose-limiting events (eg, opportunistic infection) may continue study treatment without interruption.

‡ Ophthalmologic examination includes visual acuity, fundoscopy, and slit lamp, biomicroscopy and should be performed by an ophthalmologist. Ophthalmologic examinations should be repeated during the study whenever a vision disorder AE is observed or NCI -CTCAE v4.0 grade change occurs from the previous visit.

§ If required per country-specific guidelines (eg, France): Patient management of increased ALT >3 - ≤5 x ULN (Grade 2) with a total bilirubin <2 x ULN will be discussed on a case-by-case basis between the principal investigator and an internal sponsor clinical committee (including Medical Monitor and Safety Risk Lead) and determine whether to: a. Continue treatment at the same dose level of crizotinib; b. Withhold crizotinib until ALT is Grade ≤1 or has returned to baseline, then resume treatment at the same dose level; or c. Withhold crizotinib until ALT is Grade ≤1 or has returned to baseline, then reduce the dose by 1 dose level. For patient enrolling in France, discontinue crizotinib therapy if Grade 3 and 4 ALT elevation possibly related to crizotinib with total bilirubin <2 X ULN.

5.5.2.1. Nausea and Emesis

For nausea and emesis with crizotinib, treat with standard antiemetics as per institutional standard practice. Taking the medication with food may reduce nausea. The use of prophylactic antiemetics should be considered.

5.5.2.2. Diarrhea

Grade 1: Symptomatic care with anti-diarrheal medication (such as loperamide), or no intervention as per investigator judgment.

Grade 2: Loperamide (4 mg at first onset, then 2 mg every 2 to 4 hours until symptom-free for 12 hours). Other anti-diarrheal medications can be used per local standard-of-care. No dose modification unless patient is intolerant or symptom is recurrent.

Grade 3-4 (despite use of anti-diarrheal medication such as loperamide): Withhold crizotinib (or lorlatinib) treatment until recovery to Grade ≥1.

5.5.2.3. Bradycardia

Avoid using crizotinib in combination with other bradycardic agents (eg, beta blockers, non-dihydropyridine calcium channel blockers such as verapamil and diltiazem, clonidine, digoxin) due to the increased risk of symptomatic bradycardia (syncope, dizziness, hypotension). Heart rate and blood pressure should be monitored regularly. Dose modification is not required in case of asymptomatic bradycardia. See Table 5.

5.5.2.4. Pneumonitis/Pneumonia

Investigators must evaluate thoroughly patients who demonstrate potential signs/symptoms of pneumonitis/pneumonia. If a patient has a potential diagnosis of pneumonitis or drug-related lung injury, then the following evaluations/procedures should be considered to confirm or exclude the diagnosis of pneumonitis during this period in the absence of disease progression, other pulmonary disease, infection, or radiation effects:

- A sputum gram stain and culture (induced sputum if needed) bacterial, viral, fungal, protozoal, and mycobacteria;
- Blood culture should be performed in febrile patients. Consider appropriate serologies (mycoplasma, legionella, cytomegalovirus, other viruses, etc.);
- Thoracentesis if pleural fluid is present (culture, microbiology, cytology);
- Bronchoscopy with bronchoalveolar lavage (BAL) if appropriate. The BAL fluid should be sent for culture, microbiology, and cytology (same pathogens as above);
- Lung biopsy (eg, open or thorascopic preferable, bronchoscopy with transbronchial biopsy) if appropriate;
- A plasma sample for BNP (B-type natriuretic peptide) to evaluate for evidence of congestive heart failure (CHF);

- For *Asian countries based patients*, a blood sample for β-D glucan to evaluate for the presence of fungal pneumonia (eg, Pneumocystis *jirovecii*).

If clinically appropriate, high-dose corticosteroid treatment should be initiated. Should the event be fatal an autopsy is highly recommended to confirm/exclude the diagnosis.

For any case of drug-related pneumonitis, discontinue crizotinib and contact the sponsor. See Table 5.

5.5.2.5. Renal Cysts

The development of complex renal cysts has been reported in some patients with NSCLC treated with crizotinib. These cysts may be symptomatic or asymptomatic, and have developed from 2 and 6 months after starting crizotinib. The precise nature and significance of these cysts is unclear; however, while no evidence of malignancy has been found based on aspiration of cyst fluid and biopsy in the reported cases, complex renal cysts may be associated with renal malignancy, and thus consultation with a urologist or suitable alternate medical expert is recommended.

Active surveillance with appropriate imaging (contrast-enhanced CT scanning or magnetic resonance imaging) should be performed at the time of the renal cysts diagnosis. Investigators should also review retrospectively all CT/MRIs for any prior occurrence of complex renal cysts.

In addition, multitest dipstick urinalysis (should include test for protein and blood) should be performed at the time of the renal cysts diagnosis and on Day 1 of each cycle thereafter.*

Urine reflex microscopy is required whenever urine multitest dipstick is positive for blood or protein and/or if this is the local standard.

*Additional analysis per local requirement may be performed.

5.5.2.6. Severe Visual Loss

Discontinue crizotinib in patients with severe visual loss (best corrected vision less than 20/200 in one or both eyes).

Any adverse event of Grade ≥2 of potential sight threatening (PST) or severe vision loss (SVL) that occurs in crizotinib treated patient should be treated as SAEs (Serious Adverse Events) regardless of relatedness to study drug (except for visual field defect, for which only Grade ≥3 should be treated as SAE).

Additional efforts will be made to obtain relevant clinical and diagnostic information related to all cases of Grade 4 vision loss and including an ophthalmological evaluation that should consist of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT), and other evaluations as appropriate for new onset of severe visual loss.

In addition to collecting this information as requested for Study B7461006, investigators must also be reminded of a separate data collection for crizotinib-related visual loss which is currently ongoing under the non-interventional Study A8081062.

5.6. Management of Overdose

An overdose is defined as any dose of lorlatinib >100 mg QD or any dose of crizotinib >250 mg BID. Any overdose must be recorded in the trial drug section of the CRF.

For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or not), must be reported to the sponsor (see Section 8.2.1).

Investigators should use their clinical judgment and treat potential cases of overdose with the appropriate general supportive measures.

5.7. Investigational Product Storage

The investigator, or an approved representative, (eg, pharmacist), will ensure that all investigational products, including any comparator, are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational product should be stored in its original container and in accordance with the label. Any storage conditions stated in the single reference safety document (SRSD) (ie, the IBs for lorlatinib and the CDS for crizotinib) will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

Any excursions from the product label storage conditions should be reported to Pfizer upon discovery. The site should actively pursue options for returning the product to the storage conditions described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer.

Once an excursion is identified, the investigational product must be quarantined and not used until Pfizer provides permission to use the investigational product. It will not be considered a protocol deviation if Pfizer approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to Pfizer approval will be considered a protocol deviation. Specific details regarding information the site should report

for each excursion will be provided to the site. Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

Site staff will instruct patients on the proper storage requirements for take home investigational products.

5.8. Investigational Product Accountability

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record.

All bottles of the investigational product (lorlatinib and crizotinib) are taken home by the patient, and must be returned to the investigator by the patient at the end of each cycle and at the end of the trial. The sponsor will provide instructions as to the process for drug accountability in the monitoring plan.

5.8.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study 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.

5.9. Concomitant Treatments

Concomitant treatment considered necessary for the patient's well-being may be given at the discretion of the treating physician.

Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, antiemetic treatment and prophylaxis), and the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

Medications intended solely for supportive care (eg, antiemetics, analgesics, megestrol acetate for anorexia, bisphosphonates or RANK-ligands for metastatic bone disease or osteoporosis) are allowed. In case the patient is already on treatment with RANK-ligands (like denosumab) before study entry, the therapy should be at a stable dose prior to randomization.

There are no prohibited therapies during the Post-Treatment Follow-Up Phase.

5.9.1. Inhibitors and Inducers of CYP Enzymes

The list of food and drugs to be avoided provided below may not be fully exhaustive. Consult the sponsor when in doubt whether a food or a drug falls into any of the categories below.

5.9.1.1. Arm A Lorlatinib

The *in vitro* studies have demonstrated that CYP3A, and UGT1A4 are primarily involved in the metabolism of lorlatinib, with additional minor contributions from CYP2C19 and CYP2C8. Inhibition or induction of the above enzymes may result in potential alteration of lorlatinib systemic exposure.

Initial *in vitro* assessment for inhibition and induction drug-drug interaction potential indicated that lorlatinib is a time-dependent inhibitor of CYP 3A and also an inducer of CYP3A and CYP2B6. At substantially higher concentrations than those observed clinically, lorlatinib also inhibited CYP2C9 in *in vitro* studies.

To protect patient safety, the following cautions are provided:

- Lorlatinib metabolism may be inhibited by strong CYP3A inhibitors leading to a potential increase in lorlatinib toxicities. Coadministration of strong CYP3A inhibitors (eg, boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, 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]) is not recommended and alternate medications should be considered. If the concomitant use of the strong CYP3A inhibitor cannot be avoided, reduce the starting dose of lorlatinib from 100 mg orally once daily to 75 mg orally once daily. In patients who have had a dose reduction to 75 mg orally once daily due to adverse reactions and who initiate a strong CYP3A inhibitor, reduce the lorlatinib dose to 50 mg orally once daily. The patient should be closely monitored for safety and reduction of the lorlatinib dose if necessary. If concomitant use of a strong CYP3A inhibitor is discontinued, increase the lorlatinib dose (after 3 plasma half-lives of the strong CYP3A inhibitor) to the dose that was used before starting the strong inhibitor.

- Use of strong CYP3A inducers with lorlatinib is contraindicated.
  Lorlatinib metabolism may be induced when taking strong CYP3A inducers (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort) resulting in reduced plasma concentrations. Furthermore, when lorlatinib was coadministered with rifampin, 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 (eg, bosentan, efavirenz, etravirine, modafinil) should be avoided due to the potential reduction in lorlatinib exposure.

- 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 should be used with caution, as the net clinical effect of lorlatinib on CYP2B6 is currently being investigated.

- Lorlatinib induces CYP3A (in vivo) which may lead to a decreased effect of concurrently used CYP3A substrates (eg. hormonal contraceptives etc.).

Coadministration of lorlatinib with CYP3A substrates with a narrow therapeutic index (NTI) such as alfentanil, fentanyl (including transdermal patch), astemizole*, cisapride*, cyclosporine, dihydroergotamine, ergotamine, pimozide, quinidine, sirolimus, tacrolimus, terfenadine* (*withdrawn from US market) is not permitted at study entry. However if it is absolutely necessary to use, sponsor approval is required and the dose of the CYP3A substrate may need to be increased. The NTI CYP3A 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 CYP3A substrate should be stopped and resumed at a readjusted dose only after at least 14 days of resumed lorlatinib dosing.

- Lorlatinib inhibits P-glycoprotein (P-gp) (in vitro) so concurrent use of drugs which are P-gp substrates with a narrow therapeutic index may have increased effect. 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.

Any questions regarding the use of alternative medications should be directed to the sponsor for guidance.

5.9.1.2. Arm B Crizotinib

If there is a clinical indication for one of these or other medications specifically prohibited during the trial, discontinuation from study therapy or medication may be required. The final decision on any supportive therapy rests with the Investigator and/or the patient's primary physician. However, the decision to continue the patient on study therapy or medication schedule requires the mutual agreement of the Investigator, the sponsor, and the patient.

- The metabolism of crizotinib is predominantly mediated by the CYP3A isozymes in human liver microsomes and hepatocytes. Coadministration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of crizotinib in humans. The concurrent use of potent CYP3A inhibitors, including but not limited to clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, troleandomycin, saquinavir, voriconazole, and grapefruit or grapefruit juice, are not allowed in the study. The topical use of these medications (if applicable), such as 2% ketoconazole cream, may be allowed. The concurrent use of potent CYP3A inducers, including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's wort, are not allowed in the study.

- In vitro data indicate that the most pronounced inhibitory potential of crizotinib was observed toward CYP3A4 (testosterone)-mediated drug metabolism. Crizotinib has minimal potential to inhibit other human CYP isoforms such as CYP1A2, 2C8, 2C9, 2C19 and 2D6. Crizotinib also showed time-dependent inhibition of CYP3A isozymes in human liver microsomes. In cancer patients, a mean 3.6-fold (90% CI: 2.7-4.9) increase in the oral midazolam AUC was observed following 28 days of crizotinib dosing at 250 mg BID, suggesting that crizotinib is a moderate inhibitor of CYP3A. Caution (excluding those restricted medications mentioned above) must be exercised in patients receiving crizotinib in combination with drugs that are predominantly metabolized by CYP3A such as alfentanil, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus. In particular, coadministration of crizotinib with CYP3A4 substrates with narrow therapeutic indices including, but not limited to dihydroergotamine, ergotamine, pimozide, astemizole,* cisapride,* and terfenadine* (*withdrawn from U.S. market) must be avoided from the time of the first dose of crizotinib until treatment discontinuation

5.9.2. Other Anti-Tumor/Anti-Cancer or Experimental Drugs

No additional concurrent anti-tumor treatment will be permitted while patients are receiving study treatment. Additionally, the concurrent use of select vitamins or herbal supplements is not permitted.

5.9.3. Other Prohibited Concomitant Medications and Therapies

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy.
- Investigational agents other than lorlatinib.
- Radiation therapy (with the exception noted in the Concomitant Radiotherapy Section).
- Other experimental pharmaceutical products.
- Herbal remedies with anticancer properties or known to potentially interfere with major organ function or study drug metabolism (eg, hypericin).

5.9.4. Hematopoietic Growth Factors

Use of granulocyte colony stimulating factors should follow the current American Society of Clinical Oncology (ASCO) guidelines.[32] Patients who enter the study on stable doses of erythropoietin or darbepoetin may continue this treatment, and patients may start either drug during the study at the discretion of the investigator.

5.10. Concomitant Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study.

The appropriate interval of time between surgery and crizotinib or lorlatinib administration required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping crizotinib or lorlatinib is recommended at least 2 days prior to surgery. Postoperatively, the decision to reinitiate crizotinib or lorlatinib treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery, but resumed no sooner than 48 hours after surgery.

5.11. Concomitant Radiotherapy

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at baseline, otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression.

Crizotinib must be stopped 24 hours before and at least 24 hours after completion of radiation therapy. 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.

6. STUDY PROCEDURES

As applicable, all visits must occur within the pre-defined windows outlined in this protocol.

6.1. Screening

Informed Consent must be obtained prior to undergoing any study specific procedures. Informed consent for use of tissue for other CCI [redacted] research or diagnostic development must also be obtained. In addition, Molecular Prescreening Informed Consent must be obtained in case the ALK status determination is not already available or has been obtained through a test other than the required Ventana ALK (D5F3) IHC test performed on the Ventana ULTRA or XT platforms, are acceptable, while tests performed on the GX platform cannot be accepted.

For screening procedures see the Schedule of Activities (SOA) and ASSESSMENTS section.

6.1.1. Tumor Biospecimens

Provision of an archival formalin fixed and paraffin embedded (FFPE) tumor tissue sample is required from all patients prior to registration. The archival tumor tissue specimen may be from either a primary or metastatic lesion, and may represent tissue obtained at the time of, or subsequent to, the initial diagnosis. It would be preferable if the tumor tissue was collected within 6 months of the enrollment onto the trial to provide the most up-to-date information regarding the tumor and its microenvironment. Archived tumor tissue should be

provided as a FFPE tumor tissue block containing sufficient tumor tissue to allow if possible for sectioning of at least 10 (preferably 15) slides each containing a ~5-micron tissue section.

If local country regulations do not allow for tissue block to be submitted or if a tissue block cannot be provided, sites should provide if possible at least 10 (preferably 15) unbaked glass slides each containing a ~5-micron tissue section cut serially from the same block. If archived FFPE tissue is not available, a de novo (ie, fresh) core needle tumor biopsy sample must be obtained in accord with local institutional practice for tumor biopsies. Archived or de novo tumor tissue from cytological sampling (eg, fine needle aspiration, pleural effusion, processed as FFPE block) is acceptable at screening and can be submitted. Archived or de novo tumor tissue from bone metastasis is not adequate and should not be submitted.

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Tumor core needle biopsies (2-3 cores) are preferred; pleural effusions (PE) cell pellets may substitute for tumor core biopsy as appropriate. Fine needle aspiration (FNA) samples (2-3 passes minimum prepared as FFPE cell block) should only be performed in the event a biopsy or pleural effusion cell pellet is not safe or feasible. The de novo biopsy samples should be formalin fixed and paraffin embedded as per routine (see Study Manual), and the resulting FFPE tissue block(s) should be submitted to the Central Laboratory. If the FFPE tissue block cannot be provided, a minimum of 15 unstained slides each containing a 5-micron tissue section cut serially from the block can substitute. Additional information on tumor biospecimen collection procedures is included in the Study Manual.

6.1.1.1. Determination of ALK Status

ALK status determination will be performed at screening using the FDA-approved (in US) and the CE (Conformité Européene) marked (for EU and other countries that accept CE marking), or PMDA-approved (in Japan) Ventana ALK (D5F3) CDx IHC test performed on the Ventana ULTRA or XT platforms, performed by either local or central laboratory testing. Ventana ALK (DF53) test data performed on the GX platform cannot be accepted.

Determination of ALK Status

- Patients who have historical results available showing ALK-positivity through Ventana ALK D5F3 CDx test can proceed with the screening assessments. The pathology reports to verify that the approved Ventana ALK (D5F3) CDx test was performed must be prospectively collected and sent to Pfizer for patient eligibility confirmation before proceeding to randomization.

  Where available, Ventana ALK results are only defined as “Positive” or “Negative.”

  ALK reports should be provided in English and the translation must be certified.

If the correct test verbiage (Ventana ALK (D5F3) CDx assay, or the platform (Ventana Benchmark ULTRA or XT platform) need to be added to the original ALK report, the amended report must include the signature and date of entry to confirm the information included is correct and accurate.

- Patients who have historical results available showing ALK-positivity through a non-Ventana ALK D5F3 CDx test can start the screening assessments while waiting for the Ventana ALK D5F3 CDx assay to be performed. If ALK-positivity is not confirmed, the patient is a screen failure. Re-testing time should be within the 28 days screening time
- Patients who do not have historical results available must undergo a pre-screening Ventana ALK D5F3 CDx test and, if positive, can start the screening assessments.

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6.2. Treatment Period

For treatment period procedures, see Schedule of Activities and ASSESSMENTS section.

6.3. End of Treatment/Withdrawal and Post-Treatment Follow-Up

For treatment period procedures, see Schedule of Activities and ASSESSMENTS section.

6.4. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawl From the Study Due to Adverse Events Section 8.1.3) or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Reasons for withdrawal of study treatment may include:

- Objective disease progression (either by BICR or by Investigator). However, patients with disease progression who are continuing to derive clinical benefit from the study treatment per the Investigator will be eligible to continue with lorlatinib or with crizotinib as single agent, provided that the treating physician has determined that the benefit/risk for doing so is favorable and discussed with the sponsor;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;

- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Patient refused further treatment (follow up permitted by patient);
- Study terminated by sponsor;
- Death.

Reasons for withdrawal from study follow up may include:

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

6.5. Survival Follow up Visits

For survival follow up procedures see Schedule of Activities table and ASSESSMENTS section.

If a patient does not return for a scheduled visit, every effort should be made to contact the patient. All attempts to contact the patient and information received during contact attempts must be documented in the patient's medical record. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational products, request that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved AEs.

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

7. ASSESSMENTS

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

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

7.1. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging will include chest, abdomen, and pelvis CT or MRI scans and brain MRI. CNS imaging using MRI (unless contraindicated) is required at baseline in all patients and at every tumor assessment. The response of measurable intracranial disease (ie, lesions ≥5 mm) will be assessed by a modified version of RECIST v1.1,[33] see Appendix 3. Tumor assessments are to be done at screening, then repeated every 8 weeks (±1 week) starting from randomization while on treatment and during follow-up until PD. Bone scans will be performed (or bone MRI if preferred by Investigator) at baseline and on study only if bony metastases are suspected. Patients with positive results on the bone scans (or bone MRI) will have these repeated every 16 weeks (±1 week).

Tumor assessments must continue until documented disease progression has been determined by BICR. If a patient continues treatment based on the investigator's judgement of clinical benefit in spite of disease progression- confimed by BICR- (eg, intracranial lesions are not in progression) tumor assessment must continue to be performed every 8 weeks ±1 week (16 weeks ±1 week for Bone Scan/MRI if applicable).

For patients discontinuing treatment for reasons other than progression of disease, tumor assessments must be evaluated for tumor response until PD, regardless of new anti-cancer therapy.

Both target and non-target lesions are to be followed using the same modality used at baseline and interval unless clinically indicated. Tumor assessments should be repeated after at least 4 weeks to confirm response, and at the End of Treatment visit if more than 8 weeks have passed since the last evaluation.

7.2. Expedited Blinded Independent Central Review for Disease Progression

An expedited BICR review will be performed for investigator-assessed disease progression. Upon investigator-assessed disease progression, all radiographic images collected for a patient from baseline onwards will be submitted to the BICR for expedited review (see the Study Manual for process details and maximum allowable time). Every effort should be made to keep the patient on study treatment and have all the assessments performed as per Schedule of Activities until the BICR has completed the radiographic image review, unless contraindicated by the investigator. Once the patient has documented PD by BICR, patients should be discontinued from study treatment.

However, if according to the Investigator's clinical judgment, a patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with the assigned drug after discussion between the Investigator and Pfizer. The Investigator's judgment should be based on the overall benefit/risk assessment, like the intracranial effect, and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data. In this specific circumstance (eg, intracranial lesions are not in

progression), the tumor assessments will continue to be performed every 8 weeks (every 16 weeks for bone) (±1 week) until treatment stop or as clinically indicated.

A request for an expedited BICR review may also be triggered by Pfizer upon notification of cases that have been reported as PD by Parexel during their timepoint review, but not submitted for global expedited review yet since not identified as PD cases by the investigator.

7.3. Pregnancy Testing

For female patients of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL will be performed on 2 occasions prior to starting administration of study treatment, once at the start of screening and once at the baseline visit immediately before starting the investigational product administration. Following a negative serum pregnancy test result at screening, appropriate contraception must be commenced and another negative serum or urine pregnancy test result will then be required at the baseline visit before the patient may receive the investigational product. Urine pregnancy tests will also be routinely repeated at every treatment cycle during the active treatment period, at the end of study treatment, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected. In the case of a positive confirmed pregnancy, the patient will be withdrawn from administration of investigational product but may remain in the study.

Additional pregnancy tests may also be undertaken if requested by Institutional Review Board (IRBs)/ECs or if required by local regulations.

7.4. Safety Assessments

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, 12 lead ECGs, echocardiogram/MUGA, laboratory assessments, including pregnancy tests and verification of concomitant treatments. Ophthalmologic examinations will be performed in all patients. Assessment for mood and suicidal ideation and behavior will also be performed (see Schedule of Activities).

7.4.1. Adverse Events

Assessment of AEs will include the type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.03) timing, seriousness, and relatedness.

Adverse events that occur during the study, including baseline signs and symptoms, will be recorded on the AE CRF page.

7.4.2. Laboratory Safety Assessment

Hematology, blood chemistry, and urinalysis will be collected at the time points described in the Schedule of Activities table and analyzed at local laboratories. They may also be performed when clinically indicated and relevant results reported in the CRF as ‘unplanned visits’. The required laboratory tests are listed in Appendix 4. Local laboratory certification(s) and reference ranges should be provided to the sponsor prior to study patient screening activity.

7.4.3. Vital Signs and Physical Examinations

Patients will have a physical examination to include major body systems, body weight, blood pressure, pulse rate, assessment of ECOG performance status, and height (height will be measured at screening only) at the time points described in the Schedule of Activities. Blood pressure and pulse rate should be taken with the patient in the seated position after the patient has been sitting quietly for at least 5 minutes.

7.4.4. (12-Lead) Electrocardiograms

A triplicate 12-lead (with a 10-second rhythm strip) tracing will be used for all ECG assessments, except for ECG at Day 1 of Cycle ≥3, which will be single readings according to Schedule of Activities.

All patients require a triplicate ECG measurement at screening. On treatment ECGs will be performed as outlined in the SOA table. At each time point which requires a triplicate reading per SoA, 3 consecutive 12 lead ECGs will be performed approximately 2 minutes apart (or within 10 minutes, whichever is appropriate) to determine mean QTc (average of triplicates). CCI [redacted] Clinically significant findings seen on subsequent ECGs should be recorded as adverse events. In case of QTc >500 msec (ie, CTCAE Grade >2), ECG must be reviewed by qualified personnel at the site as soon as the finding is made, including verifying that the machine reading is accurate and that the Fridericia correction formula is applied. If the manual reading verifies a rate corrected QTc of >500 msec, repeat ECG should be immediately performed at least two times approximately 2 to 4 minutes apart.

An electronic reading of prolonged QTc must be confirmed by manual reading. Prior to conclusion that an episode of prolongation of the QTc is due to study drug, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by a specialist. If QTc reverts to less than 500 msec, and in the judgment of investigator and sponsor is determined to be due to a cause other than study drug, treatment may be continued with regular ECG monitoring.

If a patient experiences PR interval prolongation >200 msec or second-degree or third-degree AV block, while on treatment with lorlatinib, refer to Section 5.5.1.2. If a patient experiences bradycardia while on crizotinib, refer to the general recommendations for crizotinib dose modification in Section 5.5.2.

If patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), triplicate ECGs should be obtained at time of the event. If the mean QTc is prolonged (>500 msec), or new or worsened AV block is noted, then ECGs should be re- evaluated by a qualified person at the institution for confirmation and repeated as clinically indicated. CCI [redacted]

CCI Additional triplicate ECGs may be performed as clinically indicated and relevant results reported in the CRF as 'unplanned visits'.

7.4.5. Echocardiograms/MUGA Scans

In order to monitor left ventricular ejection fraction (LVEF), an echocardiogram or MUGA will be performed at the time point described in the Schedule of Activities. The same method should be used at each time point.

7.4.6. Transthoracic echocardiogram (France and Germany only)

Two (2) patients receiving lorlatinib under compassionate use programme in France have been reported to have Pulmonary Arterial Hypertension (PAH), which have been diagnosed in absence of right heart catheterization. However, in one of these patients, PAH was a pre-existing condition and confounding factors were present in the other patient. In addition, 3 cases of Pulmonary Hypertension (PH) (1 not-related SAE, 1 not-related non-SAE, and 1 related non-SAE) were reported in study B7461001. No other cases were reported in approximately 900 patients treated with lorlatinib and no findings associated with pulmonary hypertension have been observed in lorlatinib nonclinical studies.

Although the current evidence does not indicate PH is a risk associated with lorlatinib treatment, investigators in Germany and France have been required, as requested by French (Agence National de Sécurité du Medicament et des produits de santé- ANSM) and German (Bundesinstitut für Arzneimittel und Medizinprodukte-BfArM) health authorities, to implement appropriate risk-reduction measures, including a trans thoracic echocardiogram (TTE) along the study treatment period for patients enrolled in these two countries.

In order to monitor pulmonary blood pressure, the condition of the heart valves, and ventricular motion, transthoracic echocardiogram (TTE) will be performed at the time points described in the Schedule of Activities. In this respect, the benefits/risks of including patients with cardiopulmonary disorders/comorbidities or risk factors should be carefully considered. In addition:

- A prompt TTE must be performed in the event of symptoms or signs suggesting PH, and all other explorations pursuant to PH diagnosis guidelines.
- Should PH occur during treatment, following multidisciplinary discussions involving a PH specialist (cardiologist or pulmonologist), consider dose reductions or even permanently discontinuing lorlatinib in the absence of haemodynamic and clinical recovery.
- Information must be provided to patients treated with lorlatinib on the new safety finding, with the recommendation to seek immediate medical attention in the event of signs suggesting PH (particularly dyspnoea and fatigue).

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7.6. CSF Collection for Lorlatinib and Crizotinib Concentration Measurements

Diagnostic CSF analysis is mandatory for patients with suspected or confirmed leptomeningeal disease/carcinomatous meningitis (LMD/CM) not visualized on MRI (optional for the remaining patients). To be performed at baseline, and if clinically safe and feasible, further CSF cytology will be performed as clinically indicated to assess anti-tumor response and to determine lorlatinib or crizotinib concentrations.

If a patient is required to undergo a lumbar puncture while on trial, an additional ~5 mL sample of CSF should be collected for determining CCI [redacted] Crizotinib and its metabolite (Arm B) concentrations. If a CSF sample is collected, CCI [redacted] at approximately the same time. The CSF concentrations of crizotinib, CCI [redacted] other potential metabolites may be determined using a validated or non-validated method. Detailed collection and shipment procedures will be provided in the Study Manual.

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7.9. Patient-Reported Outcome Assessments

PROs will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[34] and its corresponding module for lung cancer (QLQ-LC13)[35] and the EuroQol 5 dimension 5 level (EQ-5D-5L) questionnaire.[36,37] See PRO instruments included in Appendix 6.

Patients must complete all EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-5L self-assessment questionnaires in the clinic and these cannot be taken home. All scheduled assessments of the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L must be completed in the clinic prior to any other study or medical procedures.

EORTC QLQ-C30 and QLQ-LC13:

The EORTC QLQ-C30 (Version 3.0) is a published, validated, and self-administered PRO questionnaire.[34] The EORTC QLQ-C30 consists of 30 questions and includes 5 functional scales (physical, role, cognitive, emotional, and social); a global health status/global quality of life scale; 3 symptom scales (fatigue, pain, nausea and vomiting); and 6 single items that assess additional symptoms (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) and financial impact. All scales and single item measures range in score from 0 to 100. Higher scores on the functional scales represent higher levels of functioning. Higher scores on the global health status/quality of life scale represent higher health status/quality of life. Higher scores on symptom scales/items represent a greater presence of symptoms.

The EORTC QLQ-LC13 is the lung cancer-specific module of the EORTC Quality of Life Questionnaire.[35] The EORTC QLQ-LC13 consists of 13 questions and includes 1 multi-item scale and 9 single items assessing symptoms (dyspnea, cough, haemoptysis, and site-specific pain), side effects (sore mouth, dysphagia, peripheral neuropathy, and alopecia), and pain medication use. Similar to the EORTC QLQ-C30, higher scores are reflective of a greater presence of symptoms.

The EORTC QLQ-C30 and EORTC QLQ-LC13 will be administered as noted on the SOA table. Both the EORTC QLQ-C30 and QLQ-LC13 modules require about 15 minutes to complete.

EQ-5D-5L:

The EuroQol EQ-5D-5L is a patient-completed questionnaire designed to assess health status in terms of a single index value or utility score.[36,37] There are 2 components to the EuroQol EQ-5D-5L: a descriptive system in which individuals rate their level of problems (none, slight, moderate, severe, extreme/unable) in 5 areas (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a Visual Analogue Scale (VAS) in which patients rate their overall health status from 0 (worst imaginable) to 100 (best imaginable). Published weights are available that allow for the creation of a single summary score.

The EuroQol EQ-5D-5L questionnaire will be administered as noted on the SOA table. The amount of time for a patient to complete the EQ-5D-5L is estimated to be about 2 minutes.

7.10. Assessment of Mood

An assessment of mood will be administered to patients via the Beck Depression Inventory-II scale at the time points described in the Schedule of Activities table. This is a 21- item self-report scale, with each item rated by patients on a 4 point scale (ranging from 0-3). The scale includes items capturing mood (loss of pleasure, sadness, irritability), suicidal ideation, and cognitive signs (punitive thoughts, self- criticism, self-dislike, pessimism poor concentration) as well as somatic signs (appetite, sleep, fatigue, libido).

7.11. Assessment of Suicidal Ideation and Behavior

To assess suicidal ideation behaviors, the Columbia Suicide Severity Rating Scale (C-SSRS)[37] will be administered to patients at the time points described in the Schedule of Activities table. The C-SSRS is a unique, simple and short method of assessing both behavior and ideation that tracks all suicidal events and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.

7.12. Ophthalmologic Examinations

Ophthalmologic examinations for both right and left eyes will be performed at screening for all patients enrolled and should be performed by an ophthalmologist.

Ophthalmologic examinations should be repeated during the course of the study whenever a vision disorder AE is observed or CTCAE grade change occurs from a previous visit.

Best Corrected Visual Acuity and Refraction

Best corrected visual acuity will be assessed by using a standard wall or projection chart (Snellen, or another validated scale, provided that the result is converted to Snellen value) before implementing any procedures that can affect vision (eg, pupil dilation). The same chart will be used throughout the study for a specific patient, and the right eye should be tested first. The refractive error also will be determined. The ophthalmologist should ensure that patients are seated comfortably and that they do not move their head forward or backward during testing. Patients will be told that the chart contains only letters.

Biomicroscopy

Slit-lamp biomicroscopy will be performed without dilation of the pupil and should precede the administration of any pupil-dilating agent for ophthalmoscopy.

Any abnormalities (including severity) of the eyelids, conjunctivae, sclerae, corneas, anterior chambers, irises, or lens will be recorded.

Fundoscopy

Fundoscopy will be performed after pupillary dilation to examine the vitreous body, retina macula, retina non-macula (peripheral), optic nerve head, fundus and optic disc notching.

8. ADVERSE EVENT REPORTING

8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety 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.

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	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

All observed or volunteered events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events section below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the 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 subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. 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.

8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study patient/legally acceptable representative. In addition, each study patient/legally acceptable representative will be questioned about the occurrence of AEs in a non-leading manner.

8.1.3. Withdrawal From the Study Due to Adverse Events (Also See Section 6.4 Patient Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted below, and recorded on the CRF.

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each patient begins from the time the patient provides informed consent, which is obtained before the patient'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 subjects who are screen failures, the active collection period ends when screen failure status is determined.

8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a patient during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a patient 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.

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.

If a patient 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.

8.1.4.2. 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.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

If a patient 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.

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. 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. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

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.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

8.2. Definitions

8.2.1. Adverse Events

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

- Abnormal test findings;
- Clinically significant signs and symptoms;

- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

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.

8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

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

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

8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

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

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

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).

8.2.4. Hospitalization

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

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

8.3. Severity Assessment

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed below.

GRADE	Clinical Description of Severity
0	No change from normal or reference range (This grade is not included in the Version 4.03 CTCAE document but may be used in certain circumstances.)
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

8.4. Special Situations

8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study with exception of those mentioned at Section 5.5.2.6 Severe Visual Loss for Crizotinib Patients. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4.2. Potential Cases of Drug-Induced Liver Injury

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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects 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 subject's individual baseline values and underlying conditions. Subjects 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:

- Subjects 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 subjects 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 subject 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, 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, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. 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) 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 tests (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.

8.4.3. Exposure to the Investigational Product 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.

8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (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 investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product.

- 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 investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

- If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, 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 subject 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 investigational product.

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 subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.3.2. 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.

8.4.3.3. 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 subject 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.

8.4.4. Medication Errors

Other 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

8.4.4.1. Medication Errors

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

Medication errors include:

- Medication errors involving subject 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 subject.

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**.

9. DATA ANALYSIS/STATISTICAL METHODS

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.

In order to provide overall estimates of treatment effect, data will be pooled across centers. The 'center' factor will not be considered in statistical models or for subset analyses due to the high number of participating centers in contrast to the anticipated small number of patients randomized/treated at each center.

9.1. Sample Size Determination

The primary objective of the study is to demonstrate that lorlatinib (Arm A) is superior to crizotinib (Arm B) in prolonging PFS by BICR assessment per RECIST v1.1. A key secondary objective of the study is to demonstrate that lorlatinib is superior to crizotinib in prolonging OS.

The study is designed to test H_0: $HR_{PFS} \geq 1$ vs. H_A: $HR_{PFS} < 1$, where HR_{PFS} is the hazard ratio (Arm A/Arm B) of PFS.

Approximately 280 patients (140 in each arm) were to be randomized using a 1:1 ratio stratified by presence of brain metastases and ethnic origin. As of 28 February, 2019 enrollment was closed with 296 patients randomized. One hundred seventy seven (177) PFS events will be required to have at least 90% power to detect a HR of 0.611 using a one-sided stratified log-rank test at a significance level of 0.025 (one-sided), and a 2-look group-sequential design with a Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries,

The planned sample size was determined based on the assumption of a HR of 0.611 under the alternative hypothesis (under an exponential model, assumes median PFS of 11 months in the crizotinib arm and 18 months in the lorlatinib arm). The sample size further assumed a 15% drop-out rate within each treatment arm at 30 months, a non-uniform patient accrual over approximately 15 months and follow-up after the last patient is randomized of approximately 18 months.

This sample size will also allow comparison of OS between the 2 treatment arms, provided that superiority of lorlatinib over crizotinib with respect to PFS has been demonstrated. If the true HR is 0.70 under the alternative hypothesis (under an exponential model, assumes median OS of 48 months on the crizotinib arm and 68.6 months on the lorlatinib arm), a total of 198 deaths will be required to have 70% power using a one-sided stratified log-rank test at a significance level of 0.025 (one-sided), and 3-look group-sequential design with a Lan-DeMets (O'Brien-Fleming) α-spending function to determine the efficacy boundaries.

These calculations further assumed a 15% drop-out rate for OS on either treatment arm at 120 months, and a follow-up of approximately 110 months after the last patient is randomized.

The study will be considered positive if the primary objective is met as assessed by the stratified log-rank test for the primary PFS endpoint.

9.2. Analysis Sets

9.2.1. Full Analysis Set

The full analysis (FA) set will include all patients who are randomized. Patients will be classified according to the treatment assigned at randomization. The FA set will be the primary population for evaluating all efficacy endpoints and patient characteristics.

9.2.2. Safety Analysis Set

The safety analysis (SA) set will include all patients who receive at least 1 dose of study drug. Patients will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period, in which case patients will be classified according to the first study treatment received. The SA set will be the primary population for evaluating treatment administration/compliance and safety. Efficacy endpoints may be assessed in this population as well.

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9.2.4. PRO Analysis Set

The PRO analysis set is defined as patients from the FA set who completed a baseline (last PRO assessment prior to randomization day) and at least 1 post-baseline PRO assessment.

The PRO analysis set will be the primary population for the analysis of change from baseline scores and time to deterioration (TTD) in patient-reported pain, dyspnea, or cough.

9.2.5. Biomarker Analysis Set

The biomarker analysis set will include all patients in the SA set that have at least 1 screening biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers and will also be defined separately for non-paired and paired biomarkers.

9.3. Efficacy Analysis

All efficacy analyses will be performed on the FA set unless otherwise specified.

All analyses will be performed by using SAS® Version 9.1.3 or higher.

Radiographic images and clinical information collected on study will be reviewed by a BICR. BICR assessment will be used for the primary analysis of PFS and for all secondary endpoints based on radiological assessments of tumor burden (ie, OR, DR, TTR, IC-OR, IC-DR, IC-TTR and IC-TTP). PFS and OR will also be derived using the local radiologist's/investigator's assessment.

All planned sensitivity analyses will be described in the SAP.

9.3.1. Analysis of the Primary Endpoint

The primary endpoint is PFS which is defined as the time from randomization to the date of the first documentation of objective progression of disease or death due to any cause, whichever occurs first.

PFS data will be censored on the date of the last adequate tumor assessment (prior to any new anti-cancer treatment) for patients who do not have an event (PD or death), for patients who start new anti-cancer treatment prior to an event, or for patients with an event after two or more missing tumor assessments. Patients who do not have a baseline tumor assessment, or who do not have any post-baseline tumor assessments will be censored on the day of randomization, with a duration of 1 day, unless death occurred on or before the time of the second planned tumor assessment, in which case the death will be considered an event.

The primary analysis of PFS will be performed on the FA set, based on BICR assessment. A stratified log-rank test (one-sided) will be used to compare PFS time between the 2 treatment arms at the interim and/or final analyses with the overall significance level preserved at 0.025 (one-sided). The stratification factors used to conduct the stratified log-rank test for the primary analysis will include the two randomization stratification factors and additionally, as a sensitivity analysis, may include other factors, such as baseline ECOG PS, that will be specified in the SAP. PFS times associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th, and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment HRs and the corresponding 95% CIs.

Sensitivity analyses of PFS by BICR assessment will also be performed as described in the statistical analysis plan. Additionally, a Cox regression model, stratified for baseline stratification factors, will be used to explore the potential influences of the other factors on the primary PFS endpoint.

9.3.2. Analysis of Secondary Endpoints

All analyses will be performed using the FA set. The analysis of PFS will be repeated based on the Investigator's assessment.

The analyses of other tumor-related endpoints will be based on the BICR assessment, with the exception of OR that will be based both on BICR and on the investigator's assessment.

9.3.2.1. Overall Survival

Overall Survival (OS) is defined as the time from date of randomization to date of death due to any cause. Patients last known to be alive will be censored at date of last contact.

OS will be hierarchically tested for significance at the time of PFS interim/final analysis, provided the primary endpoint, PFS, is statistically significant at that analysis. In this case, OS will also be tested at 70% of the OS events (provided the first interim analysis of OS is not statistically significant) and at the OS final analysis (provided both interim analyses of OS are not statistically significant). A stratified log-rank test (one sided; using the same stratification factors used for PFS analysis) will be used at the interim and/or final analyses with the overall significance level preserved at 0.025 (one sided). OS time associated with each treatment arm will be summarized using the Kaplan- Meier method and displayed graphically where appropriate. CIs for the 25th, 50th, and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment HRs and the corresponding 95% CIs.

Sensitivity analyses to adjust for the influence of subsequent therapy on the OS may be conducted, and further details will be specified in the statistical analysis plan.

9.3.2.2. Objective Response

Objective Response (OR) is defined as a complete response (CR) or partial response (PR) per RECIST version 1.1 (see Appendix 3) recorded from randomization until disease progression or start of new anti-cancer therapy. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met. A patient will be considered to have achieved an OR if the patient has a sustained CR or PR according to RECIST version 1.1 definitions. Otherwise, the patient will be considered as a non-responder in the ORR analysis. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the ORR analysis.

The ORR on each treatment arm will be estimated by dividing the number of patients with OR (CR or PR) by the number of patients randomized to the respective treatment arm. The corresponding exact 2-sided 95% CIs will be provided. OR comparison between the 2 treatment arms will be assessed using Cochran-Mantel-Haenszel (CMH) test using the same stratification factors as for the PFS analysis.

In addition, the Best Overall Response (BOR) for each patient will be summarized by treatment arm.

9.3.2.3. Intracranial Objective Response

Intracranial Objective Response (IC-OR) is defined as above for OR but it is only based on intracranial disease in the subset of patients with at least 1 intracranial lesion.

The IC-OR will be summarized similar to how OR will be summarized as described above. If data permits, IC-OR will also be summarized in the subset of patients with at least 1 measurable intracranial lesion.

9.3.2.4. Intracranial Time to Progression

Intracranial Time to Progression (TTP) is defined as the time from randomization to the date of the first documentation of objective progression of intracranial disease, based on either new brain metastases or progression of existing brain metastases.

IC-TTP will be calculated for the FA set and for subgroups of patients with and without brain metastases at baseline. For the subgroup of patients without brain metastases at baseline only the new brain metastases will be considered events.

Differences between treatment arms will be assessed by the stratified log-rank test. IC-TTP associated with each treatment arm will be summarized using the Kaplan -Meier method and displayed graphically where appropriate. CIs for the 25th, 50th, and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment HRs and the corresponding 95% CIs. Intracranial progression events may also be analyzed by cumulative incidence functions.

9.3.2.5. Duration of Response

Duration of Response (DR) is defined, for patients with an OR per RECIST version 1.1, as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. Censoring rules for DR will follow those described above for PFS.

DR will be summarized by treatment arm using Kaplan-Meier methods and displayed graphically, where appropriate. The median DR and 95% CI for the median will be provided for each treatment arm.

9.3.2.6. Intracranial Duration of Response

The IC-DR, based on BICR, will be summarized similar to DR as described above in the subset of the FA population with an IC-BOR of CR or PR, as the time from the first documentation of intracranial objective response (CR or PR) per RECIST 1.1 based on BICR to the date of first documentation of intracranial objective progression of disease (PD) or death due to any cause. If IC-OR will be summarized in the subset of patients with at least 1 measurable intracranial lesion, a corresponding IC-DR will be provided.

9.3.2.7. Time to Tumor Response

Time to Tumor Response (TTR) is defined, for patients with a confirmed OR, as the time from the date of randomization to the first documentation of objective response (CR or PR) which is subsequently confirmed.

TTR will be summarized using simple descriptive statistics (mean, SD (standard deviation), min, max, 25th, 50th, and 75th percentiles).

9.3.2.8. Intracranial Time to Tumor Response

Intracranial TTR based on BICR is defined, for patients with a confirmed IC-OR, as the time from the date of randomization to the first documentation of intracranial objective response (CR or PR) which is subsequently confirmed.

IC-TTR will be summarized using simple descriptive statistics (mean, SD, median, min, max, Q1, Q3).

9.3.2.9. Progression-Free Survival 2

PFS2 is defined as the time from randomization to the date of progression of disease on first subsequent systemic anti-cancer therapy, or death from any cause, whichever occurs first. If no date of disease progression on first subsequent systemic anti-cancer therapy is available, patients will be censored at date of last contact. A sensitivity analysis will be conducted including the date of discontinuation from first subsequent systemic anti-cancer therapy as an event.

Differences between treatment arms will be assessed by the stratified log-rank test. PFS2 time associated with each treatment arm will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. CIs for the 25th, 50th, and 75th percentiles will be reported. The Cox proportional hazards model will be fitted to compute the treatment HRs and the corresponding 95% CIs.

9.3.2.10. Patient-Reported Outcomes

The EORTC QLQ-C30, EORTC QLQ LC13, and EQ-5D-5L will be scored according to their respective user guides/scoring manuals.[42,39]

For each treatment arm and at each time point, the number and percentage of patients who complete the EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L will be summarized in a table, as will the reasons for non-completion of these measures.

Patient-reported HRQoL, disease/treatment-related symptoms of lung cancer, and health status will be assessed. Summary statistics (mean (and SD), median, range, and 95% CI) of absolute scores will be reported for the items and subscales of the EORTC QLQ C30, the items and subscales of the EORTC QLQ-LC13, and the EQ-5D-5L VAS scale. The mean change of absolute scores from baseline (and 95% CI) will also be assessed. Line charts depicting the means and mean changes of items and subscales over time will be provided for each treatment arm.

The number and proportion of patients who improved, worsened, or remained stable for the symptom and functional domains, global QOL and single items of the EORTC QLQ-C30 and EORTC QLQ-LC13 will be summarized for each treatment arm.

Improvement, worsening, and stable categories will be determined over each cycle and summarized as an average by patient in the symptom scales, functioning scales, and in the global QOL scale. In the symptom scales, improvement is defined as a decrease of at least 10 points. In the functioning and global QOL scales improvement is defined as an increase of at least 10 points. In the symptom scales worsening is defined as an increase of at least 10 points. In the functioning scale and global QOL scales, worsening is defined as a decrease of at least 10 points. Global QOL, functioning scales, and symptom scales that have not improved nor worsened will be considered stable Osoba et al, established that a ≥10 point minimally important difference from baseline (ie, the first PRO measurement prior to initial treatment) on the scales of the EORTC QLQ-C30 would correlate with significant (moderate) change in disease symptoms and functioning.[41]

For the EQ-5D-5L health state profiles, the proportions of patients reporting “no”, “slight”, “moderate”, “severe”, or “extreme” problems will be reported at each time point.

Scales assessing pain in chest, dyspnea, and cough from the EORTC-QLQ-LC13 will be used to evaluate TTD of these symptoms. TTD in pain in chest, dyspnea, or cough individually and as a composite endpoint will be defined as the time from randomization to the first time the patient’s score shows a 10 point or greater increase after baseline in any of the 3 symptoms. Patients will be censored at the last time they completed a subscale assessment if they have not deteriorated.

TTD of the symptom subscales will be summarized using Kaplan-Meier methods. The estimated Kaplan-Meier plots will be provided, and the 1-sided log-rank test stratified by randomization stratification factors will be the primary method to compare the time to first deterioration between lorlatinib and crizotinib. The median TTD and 2-sided 95% CI for the median will also be provided based on the Brookmeyer-Crowley method.

Treatment arms will be evaluated based on the mean scores of the EORTC QLQ-C30 and EORTC QLQ-LC13 and the EQ-5D-5L utility and VAS scores obtained from longitudinal mixed-effects regression models that contain the baseline score as a covariate. Other exploratory PRO analyses may be performed subsequently as needed.

9.4. Analysis of Other Endpoints

CCI [redacted]

[redacted]

[redacted]

9.4.3. Biomarker Analysis for Secondary CCI [redacted] Endpoints

Biomarkers will be assessed separately for whole blood, serum, plasma, archival tumor tissue, and de novo tumor tissue biospecimens. In each case, summaries of baseline levels, changes from baseline (where appropriate), expression or genetic alterations will be reported. For continuous variables, summary statistics may include the mean, ratio to baseline, standard deviation, 25th, median, and 75th percentile, %CV and minimum/maximum levels of biomarker measures; for categorical variables, summary may include number and percentage, odds ratio, frequency statistics, as appropriate.

Data from biomarker assays may be analyzed using graphical methods and descriptive statistics such as Wilcoxon Signed Rank, Wilcoxon Rank Sum Test, Kaplan-Meier estimates of efficacy parameters (eg, PFS, OS) with biomarkers as a covariate, or Box plots (this list is not exhaustive.) The statistical approach will examine correlations of biomarker results with pharmacokinetic parameters and measures of anti-tumor efficacy.

CCI [redacted]

9.5. Safety Analysis

The SA set will be the primary population for safety evaluations. Summaries of AEs and other safety parameters will be provided, by treatment arm, as appropriate.

9.5.1. Adverse Events

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible (http://ctep.info.nih.gov/reporting/ctc.html).

The frequency of patients experiencing TEAEs corresponding to system organ class and MedDRA preferred term will be reported. Adverse events will be summarized by worst NCI CTCAE v4.03 severity grade and relatedness to study treatment within each treatment arm.

In all summaries, emphasis will be on TEAEs, namely, those with initial onset or that worsen in severity after the first dose of study medication.

Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.03 Grade ≥3, trial drug-related events, and serious adverse events will be considered with special attention. As appropriate, the difference in risk between treatment arms for adverse events of clinical interest may be further assessed as described in the SAP.

Detailed information collected for each adverse event will include a description of the event, duration, whether the adverse event was serious, intensity, relationship to study treatment, action taken, and clinical outcome.

9.5.2. Laboratory Abnormalities

Laboratory test results will be graded according to NCI CTCAE v4.03. The frequency of patients with laboratory test abnormalities will be summarized according to the worst grade for each laboratory test result.

For laboratory tests without an NCI CTCAE grade definition, results will be categorized as normal (within normal ranges), abnormal, or not done.

Shift tables will be provided to examine the distribution of laboratory abnormalities.

9.5.3. Electrocardiograms

All ECGs obtained during the study will be evaluated for safety. The triplicate data will be averaged, and all summary statistics and data presentations will use the triplicate averaged data. Any data obtained from ECGs repeated for safety reasons after the nominal time points will not be averaged along with the preceding triplicates.

QT intervals will be corrected for heart rate (QTc) using standard correction factors (ie, Fridericia's [default correction], Bazett's, and possibly a study-specific factor, as appropriate). Data will be summarized and listed for QT, HR, RR, PR, QRS, QTc.

Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) of corrected QT interval and other ECG parameters will be used to summarize absolute values and changes from baseline on treatment. Categorical analysis will be conducted for the maximum change from baseline in corrected QT, PR, and QRS and the maximum post-baseline corrected QT interval.

9.5.4. Left Ventricular Ejection Fraction

For patients with MUGA scans or echocardiograms, individual LVEF proportion (%) and its changes from baseline will be summarized by time point. The number of patients and the

percentage whose maximum relative decrease from baseline in LVEF is greater than 20% will be calculated.

9.5.5. Ophthalmologic Data

For the ophthalmologic data, baseline is defined as the ophthalmologic exam performed at screening.

Best-corrected visual acuity examination results: changes from baseline will be summarized/listed for all patients from the SA set with a baseline and at least one post-baseline assessment.

Biomicroscopy (Slit Lamp) and Ophthalmoscopy (Fundoscopy) Exam Results: For baseline results, percentage of patients falling into each category of the examination status (normal, abnormal: mild, abnormal: moderate, abnormal: severe, not done) will be summarized for each structure by eye. For post-baseline results, percentage of patients falling into each category of the examination status (new findings/worsening of findings, no change, improvement of findings, not done, etc.) will be summarized for each structure by eye, for all patients with a baseline and at least 1 post-baseline assessment.

Additional summaries of ophthalmologic data will be considered as appropriate and described in the SAP.

9.5.6. Mood and Suicidal Ideation and Behavior Analyses

Changes across treatment will be described according to the Statistical Analysis Plan.

9.6. Interim Analysis

The interim analysis (IA) will be performed based on the FA set. Any safety evaluation at the time of the IA will be based on the SA set.

The goals of the IA are to allow early stopping of the study for efficacy and to assess the safety of lorlatinib. The IA will be performed with all patients randomized in the study.

The study is designed to have 1 IA and the final analysis based on the primary PFS endpoint as assessed by BICR. A Lan-DeMets (O'Brien-Fleming) α-spending function is used to determine the efficacy boundaries for PFS as shown in table below (Table 6).

Table 6. Stopping Boundaries for PFS

Analysis	Number of events (Information fraction)	Z scale	p-value (1-sided)
Interim	133 (75%)	Z <-2.337	P<0.01
Final	177 (100%)	Z <-2.012	P<0.022

The IA will be performed after approximately 133 PFS events (75% of the 177 events planned at the end of the study) If the value of the test statistic exceeds the efficacy boundary ($z < -2.337$, $p < 0.01$, if the interim analysis is performed after exactly 133 events), then the study is considered to have met its primary objective. If the results of the IA indicate serious

safety concerns, the sponsor will communicate with the Health Authorities regarding stopping the clinical trial.

The secondary OS endpoint will be analyzed using a hierarchical testing procedure, provided the primary PFS endpoint is statistically significant favoring lorlatinib. A maximum of 3 analyses are planned for OS: at the time of the interim/final PFS analysis (the one that exceeded the efficacy boundary), at 70% and 100% (final OS analysis) of the 198 OS events. An α-spending function according to Lan-DeMets (O'Brien-Fleming) independent of the one used for the primary efficacy analysis will be used to preserve the 0.025 overall level of significance across the repeated testing of the OS hypotheses in the interim and final analyses. The exact nominal p-values that will need to be observed to declare statistical significance at the time of these analyses for OS will depend on the number of OS events that have been observed at the time of these analyses and the α for OS already spent at the time of earlier analyses. The trial allows for the stopping of the study for a superior OS result, provided the primary PFS endpoint has already been shown to be statistically significant favoring lorlatinib.

9.7. Data Monitoring Committee

This study will use an external data monitoring committee (E-DMC) comprised of at least 3 members with at least one having appropriate medical qualifications and one statistician.

The E-DMC will be responsible for ongoing monitoring of the safety of patients in the study and the evaluation of efficacy at the IAs according to the charter. The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer Oncology Management for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data that are not endpoints, to regulatory authorities, as appropriate.

The expected frequency of the E-DMC meetings and what will be presented or decided at the meetings will be detailed in the DMC charter.

10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigators will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer 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 subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigators and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

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

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

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

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant

correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

In addition, the study will be conducted in accordance with the protocol, and any applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, patient names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study patients. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with applicable privacy laws.

The informed consent documents and any patient recruitment materials must be in compliance with ICH Good Clinical Practice (GCP), local regulatory requirements, and legal requirements, including applicable privacy laws.

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

The investigator must ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

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

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

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 subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of lorlatinib at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within 1 month. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial 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 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 Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are 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 subject 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 pre-specified 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 synopses in which any data that could be used to identify individual patients has 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.

15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

16. REFERENCES

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Appendix 1. Abbreviations

This following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ADME	Absorption, Distribution, Metabolism and Elimiation
AE	adverse event
AIDS	Acquired Immune Deficiency Syndrome
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	Absolute neutrophils count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BAL	bronchoalveolar lavage
BBB	blood brain barrier
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BICR	Blinded Independent Central Review
BID	bis in die (twice daily)
BNP	B-type natriuretic peptide
BOR	Best Overall Response
CDx	Companion Diagnostics
C_{max}	maximum plasma concentration
C_{trough}	trough plasma concentration
CDS	Core data sheet
CE	Conformité Européene
CI	Confidence Interval
CK	Creatine kinase
CM	carcinomatous meningitis
CCI	[redacted]
CNS	central nervous system
CR	Complete response
CRF	case report form
CRM	continual reassessment method
CSA	clinical study agreement
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse

Abbreviation	Term
	Events
CV	Coefficient of variation
DDI	Drug-drug interaction
DILI	Drug-Induced Liver Injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DR	Duration of Response
DU	dispensing unit
EC	ethics committee
ECG	electrocardiogram
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EDP	exposure during pregnancy
EudraCT	European Clinical Trials Database
FA	Full Analysis
FDA	Food and Drug Administration (United States)
FFPE	formalin fixed paraffin embedded
FNA	fine needle aspiration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	High density lipoprotein
HDPE	High Density Polyethylene
HGFR	Hepatocyte Growth Factor Receptor
HIV	human immunodeficiency virus
HR	hazard ratio
HRQL	health-related quality of life
HRT	hormone replacement therapy
IA	interim analyses
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IC-OR	Intracranial Objective Response
IC-DR	Intracranial Duration of Response
IC-TTR	Intracranial Time to Tumor Response
ID	identification
IHC	Immunohistochemistry
ILD	interstitial lung disease
IND	investigational new drug application
INR	international normalized ratio
IP	Investigational product

Abbreviation	Term
IRB	institutional review board
IRT	interactive response technology
IUD	intrauterine device
IVR	interactive voice response
IWR	interactive web response
LDL	Low density protein
LVEF	left ventricular ejection fraction
LFT	liver function test
LMD	leptomeningeal disease
LPLV	last patient last visit
MRI	Magnetic Resonance Imaging
MDZ	midazolam
MUGA	multigated acquisition
N/A	not applicable
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
NTI	Narrow therapeutic index
OCT	optical coherence tomography
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PAH	Pulmonary Arterial Hypertension
PAP	Pulmonary Arterial Pressure
PCD	primary completion date
PD	Pharmacodynamics
PFS	Progression-Free Survival
P-gp	Permeability glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PK	Pharmacokinetics
PH	Pulmonary Hypertension
PI	Principal Investigator
PR	Partial response
PRO	Patient-Reported Outcome
PST	Potential Sight Threatening
PT	prothrombin time
QD	quaque die (every day)
RECIST	Response Evaluation Criteria In Solid Tumor
RNA	ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SAP	statistical analysis plan
SCL	Supply Chain Lead
SD	Stable disease

Abbreviation	Term
SD	Standard deviation
SIB	suicidal ideation and behavior
SoA	Schedule of Assessment
SOC	Standard of care
SOP	standard operating procedure
SRSD	single reference safety document
SVL	Severe Vision Loss
TEAE	treatment-emergent adverse event
T_{max}	time to reach C_{max}
TKI	Tyrosine Kinase Inhibitor
TTE	Trans Thoracic Echocardiogram
TTP	Time to Tumor Progression
TTR	Time to Tumor Response
ULN	upper limit of normal
US	United States
VAS	Visual Analogue Scale
WOCBP	Women of Childbearing Potential

Appendix 2. Eastern Cooperative Oncology Group (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

Appendix 3. RECIST Version 1.1 - Modified to Include Assessment of CNS Metastases

The determination of antitumor efficacy during this study will be based on objective tumor assessments made according to the RECIST system of unidimensional evaluation.

Measurability of Tumor Lesions

At baseline, individual tumor lesions will be categorized by the Investigator as either measurable or non-measurable by the RECIST criteria as described below.

Measurable:

Tumor lesion: Must 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 by CT scan (CT scan slice thickness no greater than 5 mm);
- 5 mm for CNS lesions provided gadolinium contrast enhanced MRI is performed with contingent slices of 1 mm;
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-Measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin, or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

NOTE: If 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 5 lesions in total representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. **Exception to this rule is in the presence of CNS metastases ≥5 mm in diameter assessed by gadolinium contrasted MRI with slices of 1 mm; up to 5 CNS lesions will be permitted in addition to 5 extracranial lesions previously noted.**[33] Target lesions should be selected on the basis of their size (lesion 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 for all target lesions will be calculated and recorded as the baseline sum longest diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment. All measurements should be performed using a caliper or ruler and should be recorded in metric notation in centimeters.

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" or "absent."

Techniques for Assessing Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical (physical) examination when both methods have been used to assess the antitumor effect of a treatment.

Definitions of Tumor Response

Target Lesions

- **Complete response (CR)** is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

- **Partial response (PR)** is defined as a ≥30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions.

- **Progressive disease (PD)** is defined as a ≥20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum of the longest dimensions recorded since the treatment started, or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

- **Stable disease (SD)** is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest dimensions since the treatment started.

Non-Target Lesions

- **Complete response (CR)** is defined as the disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

- **Non-CR/Non-PD** is defined as a persistence of ≥1 non-target lesions.

- **Progressive disease (PD)** is defined as unequivocal progression of existing non-target lesions, or the appearance of ≥1 new lesion.

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease and progressive disease.

Confirmation of Tumor Response

To be assigned a status of PR or CR, changes in tumor measurements in patients with responding tumors must be confirmed by repeat studies that should be performed ≥4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

Determination of Tumor Response by the RECIST Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. Determination of tumor response at each assessment is summarized in the following table.

Response Evaluation Criteria in Solid Tumors

Target Lesions[1]	Non-Target Lesions[2]	New Lesions[3]	Tumor 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
PD	Any response	Yes or No	PD
Any response	PD	Yes or No	PD
Any response	Any response	Yes	PD

[1] Measurable lesions only.
[2] May include measurable lesions not followed as target lesions or non-measurable lesions.
[3] Measurable or non-measurable lesions.

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

NOTE: 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 the objective progression even after discontinuation of treatment. It should also be noted that a tumor marker increase does not constitute adequate objective evidence of tumor progression. However, such a tumor marker increase should prompt a repeat radiographic evaluation to document whether or not objective tumor progression has occurred.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy before confirming the complete response status.

Appendix 4. Required Laboratory Tests

The following laboratory tests must be performed in fasted condition.

Hematology	**Chemistry Panel**	**Urinalysis[§]**	**Coagulation Tests**
Hemoglobin	ALT	Protein, glucose and blood, albumin Urine dipstick for urine protein: If positive, and clinically indicated, collect 24-hour and microscopic urinalyses (Reflex Testing) Urine dipstick for urine blood: If positive, collect microscopic urinalysis (Reflex Testing)	PT or INR
Platelets	AST		aPTT
WBC	Alkaline Phosphatase		
Absolute Neutrophils*	Sodium		
Absolute Lymphocytes*	Potassium		
Absolute Monocytes*	Magnesium		
Absolute Eosinophils*	Chloride		
Absolute Basophils*	Calcium		
	Total Bilirubin		
	BUN or Urea		
	Creatinine		
	Glucose		
	Phosphorus or Phosphate		
	Albumin		
Lipids	Total Protein	Pregnancy Tests	
Total Cholesterol	Uric Acid	For female patients of childbearing potential, serum or urine	
LDL**	Amylase^		
HDL	Gamma glutamyl transferase (GGT)		
Triglycerides			
Infections	Creatine kinase		
HBV, HCV (Screening only and if clinically indicated in case infection status is unknonwn)	C-reactive protein (CRP)		
	Lactate dehydrogenase (LDH)		
	Lipase		

°Potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, and acetaminophen levels.

^ Serum total amylase (pancreatic isoenzyme required if serum total amylase >1.5x ULN per local institutional ranges (ie, CTCAE Grade >1)).

§ Urinalysis: Dipstick is acceptable. Microscopic analyses if dipstick abnormal and/or if this is the local standard. To be repeated as clinically indicated, for example upon diagnosis of renal cysts (more frequent assessment may be performed based on local requirement). In Korea, dipstick urinalysis should be performed in all patients at screening and on Day 1 of each cycle thereafter.

* If absolute values are not reported as per local laboratory standard practice, percentages (%) are acceptable.

**A measured LDL value is preferable instead of the calculated LDL. If LDL value is calculated from Friedewald equation, this can be considered only in absence of the following circumstances: plasma triglyceride concentration exceeds 400 mg/dL (4.52 mmol/L) and in patients with dysbetalipoproteinemia (type III hyperlipoproteinemia).

ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, GGT=gamma-glutamyltransferase, HDL = High density protein, HBV=hepatitis B virus, HCV=hepatitis C virus, INR=international normalized ratio, LDH=lactate dehydrogenase, LDL =Low density lipoprotein, WBC=white blood cell.

Appendix 5. Medications with Potential PR Interval Prolongation Effect

Note that the drugs listed below are examples and this is not intended to be an all-inclusive listing (from Nada A, et al. Am Heart J 2013;165:489-500)[44]

Electrophysiologic Effects of Select Drugs on PR Interval Based on Product Labeling

Drug	Action	Indications
Affecting AV nodal conduction (PR interval		
Adenosine	Adenosine receptor	PSVT
Amiodarone	Cardiac ion channels	Antiarrhythmics
Disopyarmide		
Encainide		
Flecainide		
Moricizine		
Propafenone		
Verapamil		
Arsenic trioxide	Multiple actions	Acute promyelocytic Leukemia
Atazanavir	HIV-protease inhibitors	Antiretroviral inhibitor
Lopinavir/Ritonavir		
Saquinavir		
Digoxin	Multiple actions	Congestive heart failure
Dolasetron	5HT3 receptor antagonist	Antiemetic
Fingolimod	S1P receptor modulator	Multiple sclerosis
Lacosamide	Not fully characterized	Partial-onset seizures
Pregabalin	Not fully characterized	Neuropathic pain
Mefloquine	Plasmodicidal effects	Antimalarial

Drugs were initially screened using the PDR3D database for PR interval prolongation using terms “PR interval prolongation”, “AV block”, “AV conduction delay”, or “heart block”. Drugs were subsequently selected for inclusion on the basis on descriptions of PR interval prolongation/AVB contained with Warning or Precautions sections of drug labels.
PSVT, Paroxysmal supraventricular tachycardia.

Appendix 6. PRO Instruments

- EORTC QLQ-C30 (version 3).
- EORTC QLQ - LC13.
- EQ-5D-5L.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4

13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17.Have you had diarrhea?	1	2	3	4
18.Were you tired?	1	2	3	4
19.Did pain interfere with your daily activities?	1	2	3	4
20.Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.Did you feel tense?	1	2	3	4
22.Did you worry?	1	2	3	4
23.Did you feel irritable?	1	2	3	4
24.Did you feel depressed?	1	2	3	4
25.Have you had difficulty remembering things?	1	2	3	4
26.Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

EQ-5D-5L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑

I have slight problems walking ❑

I have moderate problems walking ❑

I have severe problems walking ❑

I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES (eg, work, study, housework, family or leisure activities)

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN/DISCOMFORT

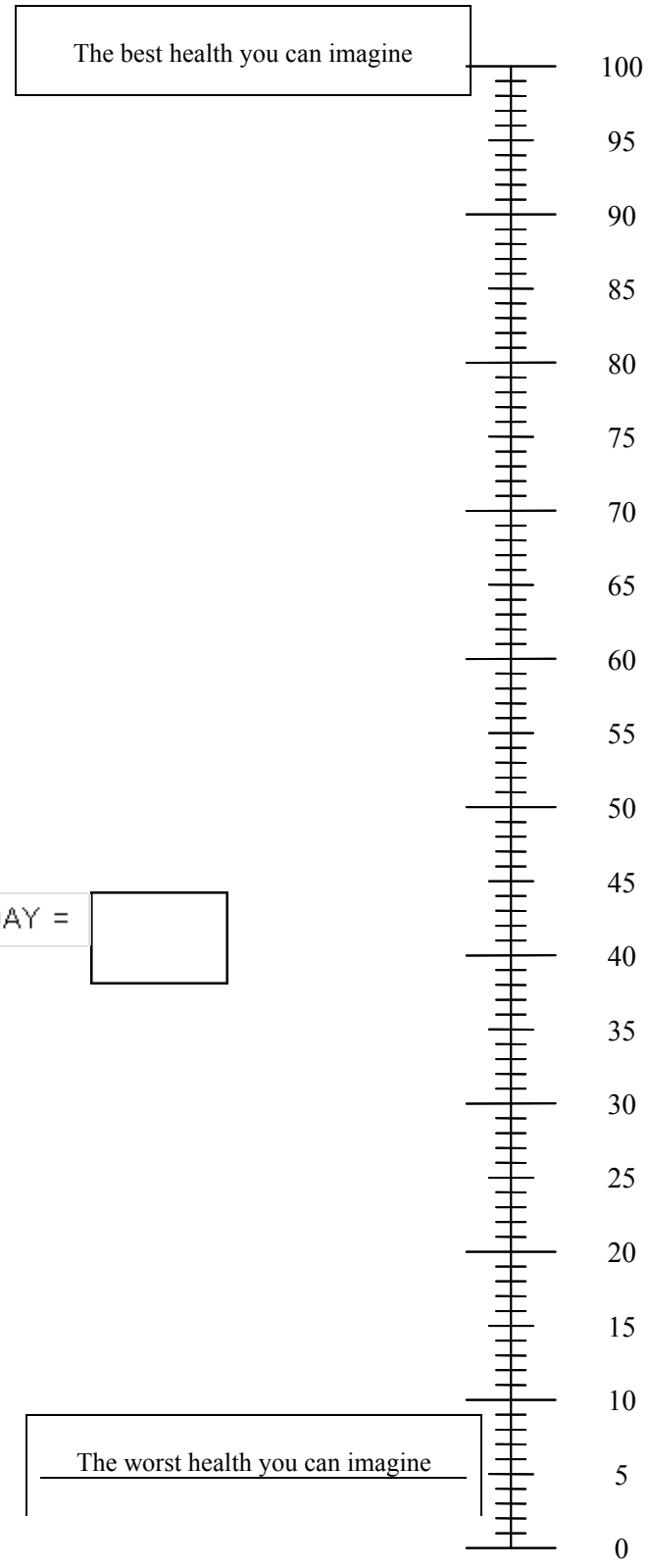
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY/DEPRESSION

I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 7. Specific for France

This appendix applies to study sites located in France.

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 investigational product.