A PHASE 2, MULTI-CENTER, OPEN-LABEL, DUAL-COHORT STUDY TO EVALUATE THE EFFICACY AND SAFETY OF LORLATINIB (PF-06463922) MONOTHERAPY IN ALK INHIBITOR-TREATED LOCALLY ADVANCED OR METASTATIC ALK-POSITIVE NON-SMALL CELL LUNG CANCER PATIENTS IN CHINA

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:	Not applicable (N/A)
Protocol Number:	B7461024
Phase:	2a

Document History

Document	Version Date	Summary of Changes and Rationale
Amendment 1	11 October 2019	• Protocol Summary updated for consistency with relevant protocol sections. • Schedule of Activities updated for consistency with relevant protocol sections. • Schedule of Activities (SOA) modified to allow use of available results for assessments performed prior to the Informed Consent being obtained. Section 7 was updated accordingly. • Time window added for Laboratory test exams in SOA: Explanatory notes and clarification for Triplicate ECG (electrocardiogram) reported in SOA. Section 7.4.4 was updated accordingly. • Time window added for Urinalysis at Screening. • Time window added for echocardiogram and multigated acquisition scan (MUGA) at screening and further assessment. • SOA footnote 14 reworded for clarity. Section 5.1 was updated accordingly. • SOA footnote 17 reworded for clarity and for consistency with Section 7. • SOA footnote 26 reworded for clarity. Section 7 was updated accordingly. • SOA footnote 27 reworded for clarity. • Section 1 background/introduction updated given the latest information of anaplastic lymphoma kinase tyrosine kinase inhibitor (ALK TKI) treatment and the update of lorlatinib clinical data. • Section 1.2.3.4 Clinical Data updated with the Study B7461001 status and safety section

		revised with regards to the updated list of lorlatinib identified risks. • Subject eligibility criteria reworded for clarity. • Inclusion Criteria #12 revised to allow urine pregnancy test at screening and reworded for clarity. • Exclusion Criteria #1 revised to define the requirement for adjuvant chemotherapy and reworded for clarity. • Exclusion Criteria #4 added to exclude patients with epidermal growth factor receptor (EGFR) activating mutations and prior therapy with EGFR TKI(s). • Exclusion Criteria #9 (#8 in the original protocol) revised to exclude prior therapy with lorlatinib. • Exclusion Criteria # 11 (#10 in the original protocol) revised to exclude patients with vascular (both arterial and venous) and non-vascular conditions. • Exclusion Criteria #12 (#11 in the original protocol) reworded for clarity. • Exclusion Criteria # 14 (#13 in the original protocol) revised to clarify that in situ malignancies which do not currently require treatment are allowed. • Exclusion Criteria #15 (#14 and #15 in the original protocol) updated to modify the list of cytochromes P450 (CYP) 3A inhibitors/inducers per new Food and Drug Administration (FDA) (United States) classification. Section 5.9.1 was updated accordingly. • Exclusion Criteria #16 (#16 in the original protocol) updated for clarity.

		• Exclusion Criteria #19 (#19 in the original protocol) updated per lifestyle guidance reported in the new Pfizer protocol template and as per contraception requirements of updated product labels. • Section 4.3 Lifestyle Requirements. This section was updated as per lifestyle guidance reported in the new Pfizer protocol template and as per contraception requirements of updated product labels which was approved. • Section 5.4.1 and Section 7.2 reworded for clarity. • A revised list of acceptable statins is provided (Section 5.5.1) to assist the Investigator in the management of patients with elevated lipid levels. • Section 5.9 (Concomitant Treatments): Text was updated to align the wording with the lorlatinib Investigator's Brochure (IB). The record duration was updated for clarity and for consistency with lorlatinib asset-level profile. SOA footnote 22 was updated accordingly. • Section 5.9.1 (Inhibitors and Inducers of CYP Enzymes) updated according to new FDA classification. • Section 5.9.3 updated and reworded for clarity. • Clarification provided in Section 7.1 and SOA for patients continuing treatment beyond disease progression. • "Central nervous system (CNS) imaging using magnetic resonance imaging (MRI) or brain computed tomography (CT) (contrast enhanced) (unless contraindicated) or" is required at baseline in all patients and at every tumor assessment" was added in section 7.1 for the sake of clarify and for consistency with response evaluation criteria in solid tumors (RECIST) 1.1 & mRECIST 1.1 in the protocol

		Appendix 3. SOA footnote 17 was updated accordingly. • Bone scan frequency in Section 7.1 changed for the safety and operational feasibility. SOA footnote 17 and footnote 27 were updated accordingly. • The frequency of tumor assessment in post treatment period in Section 7.1 will be changed to be consistent with the frequency in treatment period. SOA footnote 17 and footnote 27 were updated accordingly. • Brain CT added in Section 7.1 per RECIST 1.1 and SOA footnote 17 was updated accordingly. • Section 7.4 updated and reworded for consistency with SOA. • Clarification provided in SOA footnote 25 and Section 7.5 to improve the feasibility and precision on pharmacokinetic (PK) sample collection. • Section 7.6 reworded to clarify the sample disposition process. • Section 7.6.2 revised for consistency with the lab manual. • Section 9.1 The following text was added "In order to collect more information of anti-tumor activity, if patients received study treatment but without adequate baseline tumor assessment or without post- baseline tumor assessments, additional patients may be allowed to be enrolled". • Section 9.2 reworded as follows: "The per protocol analysis set will include all enrolled subjects with ALK positive non-small cell lung cancer (NSCLC), received a prior ALK inhibitor as protocol required, and who received at least 1 dose of lorlatinib. In Cohort 1, received crizotinib as the only ALK inhibitor.

		In Cohort 2, received one ALK inhibitor other than crizotinib, with or without prior crizotinib treatment." • Updates to Appendix 1. Abbreviation. • Updates to Appendix 4 for consistency with relevant protocol sections.
Original protocol	18 May 2018	Not applicable (N/A)

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).

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PROTOCOL SUMMARY

BACKGROUND AND RATIONALE

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total). Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer.[1] And only 18% of all patients with lung cancer are alive 5 years or more after diagnosis.[2] In China, lung cancer is also the most common cancer (0.73 million new cases) and the leading cause of cancer death (0.61 million) according to a report in 2015.[3]

In NSCLC patients, there is a clinically relevant molecular subset driven by oncogenic fusion gene EML4-ALK that combine portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and anaplastic lymphoma kinase (ALK) gene, which was discovered in 2007.[4,5]

The first approved tyrosine kinase inhibitor (TKI) for ALK-positive NSCLC was crizotinib, which has been accepted as standard of care (SOC) for ALK-positive NSCLC patients worldwide. 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 derived benefit may later develop resistance (acquired resistance). Acquired ALK kinase domain mutation and brain metastasis are the two major mechanism of refractory or resistance to crizotinib treatment.[13,14,15] For this group of patients, an alternative ALK-targeted treatment is needed.

The second-generation ALK inhibitors are being developed. Both ceritinib and alectinib showed clinical activity in crizotinib resistance and refractory NSCLC, including those with central nervous system (CNS) metastasis.[20,23] And in the subsequent Phase 3 studies, both these ALK inhibitors also showed great efficacy in treatment-naïve advanced ALK-positive NSCLC.[22,24] With this evidence, ceritinib and alectinib have both been approved in both treatment-naïve and crizotinib-resistance setting in the US by Food and Drug Administration (FDA) since 2015. In China, Xalkori® (crizotinib) and ALECENSA® (alectinib) are the standard of care (SOC) for patients with ALK-positive advanced NSCLC. For the patients previously treated with Xalkori® (crizotinib), the current SOC are ALECENSA® (alectinib) and ZYKADIATM (ceritinib) from 2018 in China.

The resistance to ALK inhibitors appears very complex as a greater variety of mutations are found in patients. To date, multiple types of ALK kinase domain mutations have been identified in crizotinib refractory patients,[16,18,19] and account for about one third of resistant samples tested. While ceritinib and alectinib are both approved for ALK-positive advanced NSCLC patients, the resistance to both of these inhibitors has also emerged. In the case of ceritinib, relapsed tumors often express the ALK mutant G1202R.[25] In the case of alectinib, in addition to G1202R, two ALK resistance mutations (V1180L and I1171T) have been observed.[25] Among these ALK mutations, ALK G1202R conferred high-level resistance to almost all of the ALK inhibitors tested.[16,18,19] In this situation, targeting on one gene

mutation won't effectively reverse the acquired resistance caused by ALK gene mutation, a broader inhibition of variety of mutations is in need for next generation of ALK TKI.

Lorlatinib is a selective, brain-penetrant ALK TKI with potent activity against ALK and ROS proto-oncogene 1(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.[27] 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.[25]

Lorlatinib has the potential to improve anti-tumor activity in ALK inhibitor resistance and ALK-positive advanced NSCLC, 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,[25] and able to cross the blood brain barrier. Lorlatinib was granted breakthrough therapy designation and priority review by FDA, and was approved by FDA in November 2018. Lorlatinib was also approved by Japan and European Union in September 2018 and in May 2019, respectively.

STUDY OBJECTIVES AND ENDPOINTS

Primary Objectives

- To evaluate the anti-tumor effect of lorlatinib as a single agent as measured by objective response rate (ORR) per response evaluation criteria in solid tumors (RECIST) v1.1 in locally advanced or metastatic ALK-positive NSCLC patients whose disease has progressed after crizotinib treatment.

Secondary Objectives

- To evaluate the anti-tumor effect of lorlatinib as a single agent as measured by ORR per RECIST v1.1 in locally advanced or metastatic ALK-positive NSCLC patients whose disease has progressed after ALK inhibitor treatment other than crizotinib.

- To evaluate the progression-free survival (PFS) and overall survival (OS) in locally advanced or metastatic ALK-positive NSCLC patients whose disease has progressed after crizotinib and other ALK inhibitor treatment, respectively.

- To evaluate other antitumor activities in locally advanced or metastatic ALK-positive NSCLC patients whose disease has progressed after crizotinib and other ALK inhibitor treatment, respectively.

- To evaluate the safety and tolerability of lorlatinib treatment in locally advanced or metastatic ALK+ NSCLC patients whose disease has progressed after crizotinib and other ALK inhibitor treatment.

- To evaluate the pharmacokinetics (PK) of lorlatinib and potential pharmacokinetic (PK)/pharmacodynamics relationship for lorlatinib if appropriate.

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- [redacted]

Primary Endpoint

- Objective Response (OR) in patients whose disease has progressed after crizotinib (Cohort 1) as assessed by Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1 per independent central radiology (ICR) assessment.

Secondary Endpoints

- OR in patients whose disease has progress after ALK inhibitor treatment other than crizotinib (Cohort 2) as assessed by RECIST v1.1 per ICR assessment.
- Progression-free survival (PFS) as assessed by RECIST v1.1 per ICR assessment and investigator assessment, and Overall survival (OS) in both Cohorts.
- Intracranial Objective Response (IC-OR), Duration of response (DoR), Duration of intracranial response (IC-DoR), Time to tumor response (TTR) as assessed by RECIST v1.1 per ICR assessment and investigator assessment, in both Cohorts.
- Safety: adverse event (AE); laboratory abnormalities; electrocardiography (ECG), left ventricular ejection fraction (LVEF), CNS effects.
- PK parameters on Day 1 of Cycle 1 and at steady state: C_{max} (maximum serum concentration), T_{max} (time to reach the maximum concentration), AUC_t (area under the plasma concentration versus time profile from time 0 to time t), AUC_{tau} (area under the plasma concentration versus time profile within a dose interval) at steady state. AUC_{inf} (area under the plasma concentration versus time curve to infinity), CL/F (oral plasma clearance), and V_z/F (apparent volume of distribution) and $t_{1/2}$ (terminal elimination half-life), R_{ac} (accumulation ratio) as data permit.

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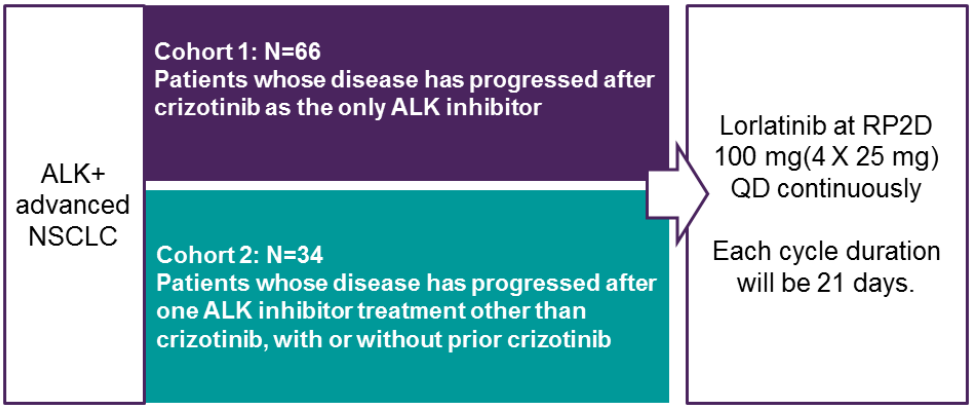
STUDY DESIGN

Study overview

This is a Phase 2, multicenter (at approximately 30 sites), dual-cohort study in China, in which approximately 100 patients with locally advanced or metastasis ALK-positive NSCLC will be enrolled to receive lorlatinib monotherapy. In Cohort 1 approximately 66 patients whose disease has progressed after crizotinib will be enrolled, and in Cohort 2, approximately 34 patients whose disease has progressed after ALK inhibitor other than crizotinib. The study design is illustrated below.



Study Treatments

All the patients enrolled into the study will receive 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.

The study treatment may continue until disease progression confirmed by independent central radiology (ICR) review, global deterioration of health status requiring permanent discontinuation per the investigator's judgement, unacceptable toxicity, pregnancy, significant protocol violation, patient lost to follow-up, or patient refusal, the study is terminated by the sponsor, or the death, whichever comes first.

Statistical Methods

The study will evaluate safety and efficacy for lorlatinib in both Cohort 1 and Cohort 2. Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be maintained by Pfizer.

Sample Size Determination

The primary objective of the study is to evaluate the anti-tumor effect of lorlatinib as a single agent as measured by ORR per RECIST v1.1 in locally advanced or metastatic ALK-positive NSCLC patients whose disease has progressed after crizotinib treatment, ie, Cohort 1.

As of the original version date of protocol, given there's no ALK TKI other than crizotinib approved in China currently, chemotherapy is still considered as standard of care for patients whose disease have progressed after crizotinib. Based on the current reported results, the ORR of chemotherapy in previous systemic treatment treated patients ranged from 6.9% - 20%.[21,28,29] The ORR was 26.7% even for treatment naive patients.[22] Therefore, ORR of 30% was chosen as the historical control for Cohort 1. The Fleming single stage design will be used to test the null hypothesis (H0) of ORR ≤30% with 1-sided 0.025 significance level. Assume at least 20% increase of ORR with lorlatinib treatment, 66 patients will be required to provide 90% power to reject the null hypothesis. Exact test will be performed at the time of the analysis. If at least 28 or more responses are observed among the 66 patients enrolled, then the null hypothesis will be rejected, and it will be concluded that the study has demonstrated that the true ORR exceeds 30%. However, at the time of the analysis, the testing will depend on the exact number of patients enrolled.

Cohort 2 will explore the safety and efficacy of lorlatinib in patients with locally advanced or metastasis ALK-positive NSCLC whose disease have progressed after one ALK inhibitor treatment other than crizotinib. As of the original version date of protocol, there was no approved ALK inhibitor other than crizotinib in China, therefore, the eligible patients were very limited and no established standard of care was available. Considering this limitation, Cohort 2 will be exploratory with about 34 patients planned to be enrolled. No specific statistical hypothesis will be tested. Descriptive analyses will be provided for the endpoints. The sample size of 34 patients will provide the estimated ORR with a maximum width of the 95% CI (confidence interval) of 35%, observed with 17 responses out of 34 patients. In order to collect more information of anti-tumor activity, if the patients received study treatment but without adequate baseline tumor assessment or without post baseline tumor assessments, additional patients may be allowed to be enrolled.

With approximately 66 and approximately 34 patients in Cohort 1 and 2 respectively, this study will provide adequate sample size for safety evaluation with a minimal number of 100.

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 on the schedule of activities table, in order to conduct evaluations or assessments required to protect the well-being of the subject.

		CYCLE 1 21 days				CYCLE 2 21 days	CYCLES ≥3 (21 days per cycle)	END of TREATMENT (EOT)/ FOLLOW-UP		
Visit Identifier[a]	**Screening**[1] **(≤28 days)**	**Day 1**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment/ Withdrawal**[26]	**Post-Treatment Follow- Up**[27]	**Survival Follow-Up**[28] **(every 4 months up to 3 years, then every 6 months)**
Visit Time Window (days)	N/A		±3	±1	±1	±2	±2	±3	±7	±7
Informed consent[2]	X									
Tumor history, including ALK status determination	X									
Medical/oncological history (incl. prior medications)	X									
Physical examination (PE)	X	X				X	X	X	X	
Baseline signs and symptoms[3]		X								
Height	X									
Weight	X	X		X	X	X	X	X		
Vital signs[4]	X	X		X	X	X	X	X	X	
ECOG performance status[5]	X	X				X	X	X		
Contraception check[6]	X	X		X	X	X	X	X	X (at 30,60,90 days)	
Laboratory										
Hematology[7]	X	X (-7 days)		X	X	X	X	X	X (at 30 and 60 days)	

		CYCLE 1 21 days				CYCLE 2 21 days	CYCLES ≥3 (21 days per cycle)	END of TREATMENT (EOT)/ FOLLOW-UP		
Visit Identifier[a]	**Screening**[1] **(≤28 days)**	**Day 1**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment/ Withdrawal**[26]	**Post-Treatment Follow- Up**[27]	**Survival Follow-Up**[28] **(every 4 months up to 3 years, then every 6 months)**
Visit Time Window (days)	N/A		±3	±1	±1	±2	±2	±3	±7	±7
Blood Chemistry[8]	X	X (-7 days)		X	X	X	X	X	X (at 30 and 60 days)	
HBV, HCV (if applicable)	X									
Lipids[9]	X	X (-7 days)		X	X	X	X	X	X (at 30 and 60 days)	
Coagulation[10]	X	X (-7 days)						X	X (at 30 and 60 days)	
Urinalysis[11]	X	X (-7 days)				X (as clinically indicated)	X (as clinically indicated)	X	X (at 30 and 60 days)	
Pregnancy test[12]	X	X				X	X	X	X (at 30 and 60 days)	
Triplicate (12-lead) ECGs[13]	X	X		X	X	X	X (single reading, pre-dose, on Day 1 of every other cycle)	X	X (at 30 and 60 days)	
LVEF assessment (Echocardiogram or MUGA scan)[15]	X	X (pre- dose- not to be repeated if normal and performed <2 weeks prior to enrollment)					X (pre dose, Day 1 of every other cycle; a time window of 1 week prior to Day 1 is permitted)	X	X (at 30 and 60 days)	
IRT Registration and Study Treatment										
IRT Registration[14]	X	X	→							
Lorlatinib		orally on a continuous QD dosing schedule								
Treatment compliance check[16]			X							

		CYCLE 1 21 days				CYCLE 2 21 days	CYCLES ≥3 (21 days per cycle)	END of TREATMENT (EOT)/ FOLLOW-UP		
Visit Identifier[a]	**Screening**[1] **(≤28 days)**	**Day 1**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment/ Withdrawal**[26]	**Post-Treatment Follow- Up**[27]	**Survival Follow-Up**[28] **(every 4 months up to 3 years, then every 6 months)**
Visit Time Window (days)	N/A		±3	±1	±1	±2	±2	±3	±7	±7
Tumor Assessments										
CT or MRI scan [17]	X	• every 6 weeks (±1 week) for CT or MRI scan • every 18 weeks (±1 week) for bone scan (or bone MRI if preferred by investigator) **only** if evidence of bone metastases is observed at baseline						X	X (every 6 weeks ±1 week, until ICR PD; If applicable, every 18 weeks (±1 week) for bone scan (or bone MRI if preferred by investigator)	X (as clinically indicated)
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CCI										

		CYCLE 1 21 days				CYCLE 2 21 days	CYCLES ≥3 (21 days per cycle)	END of TREATMENT (EOT)/ FOLLOW-UP		
Visit Identifier[a]	**Screening[1] (≤28 days)**	**Day 1**	**Day 5**	**Day 8**	**Day 15**	**Day 1**	**Day 1**	**End of Treatment/ Withdrawal[26]**	**Post-Treatment Follow- Up[27]**	**Survival Follow-Up[28] (every 4 months up to 3 years, then every 6 months)**
Visit Time Window (days)	N/A		±3	±1	±1	±2	±2	±3	±7	±7
Other Clinical Assessments										
Serious and non-serious adverse event monitoring[21]	X	X	→			→	→	→	→	
Concomitant medications and treatments[22]	X	X	→			→	→	→	→	X (subsequent systemic anticancer treatment)
Mood assessement[23]		X				X	X (up to Cycle 6 and then Day 1 of every other cycle)	X		
Suicidal Ideation and Behavior[24]		X				X	X (up to Cycle 6 and then Day 1 of every other cycle)	X		
Survival status[28]										X
Other Samples										
Pharmacokinetic Sampling[25]	See footnote[25]									

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; CT = computed tomography; MRI = Magnetic Resonance Imaging; EORTC = European Organization for Research and Treatment of Cancer; ICR= Independent Central Radiology; 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; QD = Quaque Die (every day); CCI N/A = Not applicable.

Footnotes:

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

1.	**Screening**: To be obtained within 28 days prior to enrollment (Cycle1Day1: C1D1). Available results for assessments that have been performed prior to informed consent being obtained as part of the patient's on-going routine standard of care testing (laboratory tests or tumor imaging scans) may be used to satisfy patient eligibility assessment, provided they have been performed within the required timing (that is 7 days prior enrollment for laboratory tests or 28 days prior enrollment for tumor imaging or 6 weeks prior enrollment for bone scan [or bone MRI if preferred by investigator]) and meet the related criteria.
2.	**Informed Consent**: Must be obtained prior to undergoing any study-specific procedures. CCI [redacted]
3.	**Baseline Signs and Symptoms**: Subjects will be asked about any signs and symptoms experienced within the 14 days prior to Day 1 of Cycle 1.
4.	**Vital Signs**: Include blood pressure, pulse rate, body temperature, and body weight. Blood pressure and pulse rate to be recorded in sitting position after the subject has been sitting quietly for at least 5 minutes. Body weight to be recorded at Day 1 of each cycle.
5.	**Performance Status**: according to Eastern Cooperative Oncology Group (ECOG) classification (see Appendix 2).
6.	**Contraception check:** Fertile male subjects and female subjects who are of childbearing potential will need to follow the contraception guidelines in Section 4.3.1.
7.	**Hematology**: Required tests are listed in the Appendix 4 of the protocol. May also be performed when clinically indicated (results to be entered in CRF as unplanned visit). No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date.
8.	**Blood Chemistry**: Required tests are listed in Appendix 4 of the protocol. May also be performed when clinically indicated (results to be entered in CRF as unplanned visit). No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date.
9.	**Lipids**: Required tests are listed in the Appendix 4 of the protocol. May also be performed when clinically indicated (results to be entered in CRF as unplanned visit). No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date.
10.	**Coagulation**: Required tests are listed in the Appendix 4 of the protocol. May also be performed when clinically indicated (results to be entered in CRF as unplanned visit). No need to repeat on C1D1 if baseline assessment performed within 7 days prior to that date.
11.	**Urinalysis:** Dipstick is acceptable. Microscopic analyses if dipstick abnormal and/or if this is the local standard. Not to be repeated at C1D1 if performed within 7 days before.
12.	**Pregnancy Test:** For female subjects 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 and once at the baseline visit, 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 study therapy 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.
13.	**Triplicate 12-lead ECGs**: At each time point, 3 consecutive 12-lead ECGs performed approximately 2 minutes apart (or within 10 minutes, whichever is appropriate) to determine PR interval and mean QTc interval. The ECG must occur prior to any blood sample collections or venipuncturing if conducted on the same day, except for the specific requirement in the protocol. ECGs are to be collected at predose 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. Single reading ECG are to be collected pre-dose on Day 1 of Cycle 3 and every other cycle thereafter. ECGs at later cycles are to be collected as clinically indicated. At End of Treatment/Withdrawal, triplicate ECGs are to be collected. Additional ECG time points may be performed based on the emerging data.
14.	**IRT registration:** Study treatment should be initiated preferably on the randomization day but no later than 1 days after randomization.
15.	**Left ventricular ejection fraction (LVEF) Assessment:** Echocardiogram (ECHO) or multigated acquisition scan (MUGA) to be performed at Screening, at pre-dose, on Cycle 1 Day 1 and every other cycles 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 Day 1 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.

16. **Treatment compliance check:** The study site must follow up (for example, via a telephone call) with each subject on Cycle 1 Day 5 (±3 days) to confirm that the subject understands and is in compliance with lorlatinib dosing instructions.
17. **Tumor Assessments:** to include all known or suspected disease sites. Imaging to include chest, abdomen, and pelvis CT or MRI scans; brain MRI; bone scan (or bone MRI if preferred by investigator). Brain MRI (Gadolinium contrast enhanced) or brain CT (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. CNS imaging using MRI or CT (contrast enhanced is preferred unless contraindicated) is required at baseline in all patients and at every tumor assessment. Bone scans (or bone MRI if preferred by investigator) to be performed at baseline for all subjects and repeated every 18 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 6 weeks ±1 week starting from the first dose of the investigational product while on treatment during post-treatment follow-up period until documented progression of disease by ICR. During post-treatment follow-up period, if applicable, bone scan (or bone MRI if preferred by investigator) to be performed every 18 weeks ±1 week until documented progression of disease by ICR. The responses will be required to be confirmed ≥4 weeks after the initial response is observed. Tumor assessment should be repeated at the EOT visit if more than 6 weeks have passed since the last evaluation. Tumor assessments must continue until documented progression of disease by independent central radiology review. Subjects who discontinue treatment without PD should be followed until PD confirmed by independent central radiology review 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.[31] Refer to Section 7.1 for the more details.
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[redacted]
21. **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. The time period for actively eliciting and collecting AEs and Serious Adverse Events (SAEs) ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject'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. During the active collection period, both non-serious AEs and SAEs are recorded on the case report form (CRF). If a subject begins a new anticancer therapy, the AE reporting 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.

22. **Concomitant Medications and treatments**: All concomitant medications and treatments will be recorded in the CRF from 28 days prior to enrollment and up to 28 days after the last dose of study treatment.
23. **Mood Assessment**: An assessment of mood via the Beck Depression Inventory II (BDI II) scale will be administered to subjects prior to the first day of lorlatinib dosing (ie, Cycle 1 Day 1) 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 subjects prior to the first day of lorlatinib dosing (ie, Cycle 1 Day 1) 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. **Pharmacokinetics Sampling**: Blood samples will be collected at pre-dose and 1-2 hours post-dose in on Day 1 of Cycles 2 to 5 in all subjects. Additionally, in up to 16 subjects (to acquire no less than 12 evaluable PK profiles), blood samples will be collected on Day 1 and Day 15 of Cycle 1 at the following time points: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 9, and 24 hours. Note: 1) When collecting the serial PK sample at 8 hour and 9 hour, if the actual collection time of the 8 hour sample is nearing the 9 hour nominal time (within the 10% window of the 9 hour collection time), the 9 hour sample should still be collected after the 8 hour sample and as close to the 9 hour nominal time as possible. 2) In the event of any dose interruption in 15 day time period prior to Day 15 of Cycle 1, the planned intensive PK sampling schedule on C1D15 is suggested to be extended to the Day 1 of next cycle.
26. **End of Treatment (EOT) Visit**: Obtain these assessments if not completed in the last 7 days (last 6 weeks for tumor assessments). EOT visit should be performed no later than 4 weeks (+1w) from the last dose of investigational product or when decision taken to provide alternative anti-cancer therapy, whichever is sooner. Subjects continuing treatment after disease progression confirmed by independent central radiology review will continue to perform safety assessment required in the treatment period, until treatment discontinue, and tumor assessment will be in need when clinically indicated.
27. **Post-Treatment Follow-Up Visits**: Subjects continuing to experience toxicity at this point will continue to be followed (the test/examination related to continuing adverse event(s) will be followed) at least every 4 weeks (except for the tumor assessment which will be performed every 6 weeks ±1 week, if applicable) until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected. Subjects discontinuing treatment for reasons other than progression of disease will continue to perform tumor assessments every 6 weeks ±1 week [if applicable, bone scan (or bone MRI if preferred by investigator) to be performed every 18 weeks ±1 week] until PD documented by ICR, regardless of subsequent anti-cancer treatments.
28. **Survival Follow-Up**: After discontinuation of study treatment, information on post-study survival status and subsequent systemic anti-cancer treatment (including administration dates, reason for treatment discontinuation and date of progression, if applicable) will be collected every 4 months up to 3 years, then every 6 months until death, or subject withdrawal of consent or study closure (as defined in the SAP), whichever occurs first (telephone contact is acceptable for subjects refusing/unable to go back to the site).

1. INTRODUCTION

1.1. Mechanism of Action/Indication

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

The mechanism of action of lorlatinib is described in Section 1.2.3.

1.2. Background and Rationale

1.2.1. NSCLC

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths (18.2% of the total). Non-small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer.[1] And only 18% of all patients with lung cancer are alive 5 years or more after diagnosis.[2] In China, lung cancer is also the most common cancer (0.73 million new cases) and the leading causes of cancer death (0.61 million) according to report in 2015.[3]

In NSCLC patients, there is a clinically relevant molecular subset is driven by oncogenic fusion gene EML4-ALK that combine portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and anaplastic lymphoma kinase (ALK) gene, which was discovered in 2007.[4,5]

The first approved tyrosine kinase inhibitor (TKI) for ALK-positive NSCLS was crizotinib, which has been accepted as standard of care (SOC) for ALK-positive NSCLC patients worldwide. 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%.[6]

1.2.2. ALK Alternation and Resistance Mechanism in NSCLC

Since the discovery of ALK-EML-4 fusion gene within chromosome 2p, a subsequent series of studies have described 9 fusion variants of EML4-ALK plus additional but less common fusion partners with ALK.[7] Currently, there are at least 27 different ALK fusion variants reported in the literature, while the majority of the isoforms involve EML4-ALK fusion gene, which is reported to be 3%-5% in all NSCLC patients, who tend to be young (average age 50 years at diagnosis), and light or never smokers.[8] In China, the proportion of EML4-ALK fusion in NSCLC is found to be 5.6% which is similar to that of western patient population.[9]

Oncogenic fusions of ALK and ROS1 define 2 distinct subsets of human lung adenocarcinomas[4,10] 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.[11,12]

Crizotinib, as the first-generation selective adenosine triphosphate (ATP)-competitive small-molecule inhibitor of ALK, ROS1,c-MET receptor tyrosine kinase and their oncogenic variants, demonstrated significant clinical benefit in ALK and ROS1 fusion-positive lung cancers.[11,12] This clinical benefit led to the approval of the US approval in August 2011 of Xalkori® (crizotinib) in advanced ALK-positive NSCLC patients. And subsequently, Xalkori® was approved in European Union (EU) and Japan. In 2013, Xalkori® received approval by China Food and Drug Administration (CFDA) in treatment of ALK-positive advanced NSCLC in China.

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 derived benefit may later develop resistance (acquired resistance). Acquired ALK kinase domain mutation and brain metastasis are the two major mechanism of refractory or resistance to crizotinib treatment[13,14,15] for this group.

The resistance to ALK inhibitors appears much more complex as a greater variety of mutations are found in patients along with the activation of bypass resistance mechanisms.[16,17] To date, multiple types of ALK kinase domain mutations have been identified in crizotinib refractory patients including ALK^{G1269A}, ALK^{L1196M}, ALK^{C1156Y}, ALK^{L1152R}, ALK^{F1174L}, ALK^{G1202R}, ALK^{S1206Y}, $ALK^{1151Tins}$ and ALK gene amplification,[16,18,19] and account for about one third of resistant samples tested. Among these ALK mutations, ALK^{G1202R} conferred high-level resistance to almost all of the ALK inhibitors tested.[16,18,19] In the case of crizotinib resistant ALK-positive NSCLC patients, the rate of resistance due to mutations in the ALK kinase domain is typically reported in the range of 35-40%.[16] While other mechanisms of resistance (independent of ALK mutation) are active, the tumor cell may still remain dependent upon ALK signaling. It was also reported that the brain was the most common single site of disease progression (>30%) following initial crizotinib treatment.[14,15] It is unknown if this is due to the formation of resistance mutations or the intact blood brain barrier (BBB) creates a sanctuary site preventing the passage of crizotinib. Finally another roughly 5% of patients acquire resistance through amplification of the EML4-ALK fusion gene.[16]

To fulfill this treatment need in ALK-positive advanced NSCLC patients, second-generation of ALK inhibitors have been developed and showed treatment activity.

Ceritinib (Zykadia™) is the first second-generation ALK inhibitor to show clinical activity.[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. Subsequently, in global Phase 3 studies, Ceritinib showed superior efficacy compared to chemotherapy in both treatment naïve and

crizotinib refractory advanced ALK-positive NSCLC patients, and gain approval in all ALK-positive metastatic NSCLC patients in 2017.[21,22]

Alectinib (Alecensa™) is a selective ATP-competitive ALK inhibitor, and has showed clinical activity in patients previously treated with crizotinib, including those with CNS metastasis. In this study, among 35 patients with baseline measurable CNS lesion, the CNS ORR was 57%.[23] Basing on this result, alectinib received accelerated approval by FDA in the US in 2015. In further, in a Phase 3 study of alectinib compared to crizotinib in treatment-naïve advanced NSCLC, alectinib show superior efficacy, with a significantly longer PFS,[24] which lead to approval of alectinib for treatment-naïve ALK-positive advanced NSCLC.

While ceritinib and alectinib are both approved for ALK-positive advanced NSCLC patients, the resistance to both of these inhibitors has also emerged. In the case of ceritinib, relapsed tumors often express the ALK mutant G1202R.[25] In the case of alectinib, in addition to G1202R, two ALK resistance mutations (V1180L and I1171T) have been observed.[25] Some ALK mutants such as G1202R confer high-level resistance to all clinically available ALK inhibitors. Both ceritinib and alectinib have demonstrated activity in brain metastases of crizotinib-relapsed patients. A Phase 1/2 clinical trial of alectinib showed a CNS response rate of 52%. Despite the observed CNS activity with these agents, it remains common for patients to relapse with CNS progression.[25]

Currently in China, there are several ALK inhibitors being developed in different stages in both treatment-naïve and crizotinib-resistant ALK-positive advanced NSCLC settings, such as alectinib (NCT02838420), ceritinib (NCT02040870), ensartinib (NCT02959619), X-396 (NCT03215693), PLB1003 (NCT03130881), CT-707 (NCT02695550) etc. Xalkori® (crizotinib) and ALECENSA® (alectinib) are the SOC for ALK-positive advanced NSCLC patients. For the patients previously treated with Xalkori® (crizotinib), the SOC are ALECENSA® (alectinib) and ZYKADIATM (ceritinib) from 2018 in China.

1.2.3. 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.[25]

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.[27] Lorlatinib was granted breakthrough therapy designation and priority review by FDA, and was approved by FDA in in November 2018. Lorlatinib was also approved by Japan and European Union in September 2018 and in May 2019, respectively.

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 1.2.3.4.

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

1.2.3.1. 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 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-base assays. Lorlatinib 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-ALKL1196M or EML4-ALKG1269A mutations. Lorlatinib treatment significantly reduced tumor size and prolonged animal survival in the orthotopic brain models (EML4- ALK and EML4-ALKL1196M) 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/pharmacodynamics modeling, ADME (Absorption, Distribution, Metabolism and Elimination), and cytochromes P450 (CYP) enzymes inhibition can be found in Section 1.2.3.3 and the lorlatinib IB.

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

1.2.3.2. 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 may be found in the IB.

1.2.3.3. Pharmacology

1.2.3.3.1. Metabolism

Lorlatinib undergoes oxidation and glucuronidation as the primary metabolic pathways. Oxidative metabolism of lorlatinib is primarily mediated by CYP3A4 with minor contributions from CYP2C19, CYP2C8, and CYP3A5. Glucuronidation of lorlatinib is mediated primarily by uridine 5'-diphospho-glucuronosyltransferase (UGT)1A4, with minor contribution from UGT1A3.

1.2.3.3.2. Clinical Drug-Drug Interaction

In vitro, lorlatinib is a time-dependent inhibitor as well as an inducer of CYP3A4/5 and activates the human pregnane X receptor (hPXR), with a net induction effect on CYP3A4/5 in vivo. Coadministration of lorlatinib and midazolam (MDZ) in patients resulted in decreased mean oral MDZ (a CYP3A4 substrate) AUC and C_{max} after 25 mg and 150 mg QD lorlatinib dosing, compared with those for MDZ alone. Coadministration of lorlatinib with CYP3A4/5 substrates with narrow therapeutic indices should be avoided.

Coadministration of 200 mg daily doses of itraconazole (a strong CYP3A4/5 inhibitor) with a single 100 mg of lorlatinib increased lorlatinib AUC_{inf} by 42% and C_{max} by 24%. An alternative concomitant medicinal product with less potential to inhibit CYP3A4 should be considered. If a strong CYP3A4/5 inhibitor must be coadministered, a dose reduction of lorlatinib from the starting dose of 100 mg QD to 75 mg QD is recommended.

Coadministration of 600 mg daily doses of rifampin (a strong CYP3A4/5 inducer) with a single 100 mg dose of lorlatinib decreased lorlatinib AUC_{inf} by 85% and C_{max} by 76%. Concomitant administration of lorlatinib and rifampin led to elevated AST and ALT levels in all subjects. Use of strong CYP3A4/5 inducers with lorlatinib is contraindicated. Avoid concomitant use with moderate CYP3A4/5 inducers if possible, as they may also reduce lorlatinib plasma concentrations.

1.2.3.3.3. Exposure-Response Relationship

No exposure response (E-R) relationship was observed between lorlatinib plasma exposure and efficacy endpoints (objective response rate [ORR], intracranial objective response rate [IC-ORR]) in patients who received ≥1 or ≥2 prior ALK inhibitors.

A statistically significant E-R relationship of safety was observed for Grade ≥3 HYPERCHOLESTEROLEMIA and any Grade ≥3 treatment-emergent all-causality adverse events (AEs), with higher probability of the occurrence of these events with increasing lorlatinib plasma exposure.

An itraconazole drug interaction study (Study B7461012) was conducted as an alternative to a thorough QT (TQT) study. E-R analyses for Holter Monitoring data from this study indicate that there was no relationship between lorlatinib plasma concentration and the RR interval and no evidence of Corrected QT Interval (QTc) prolongation associated with lorlatinib plasma concentrations. Increase in lorlatinib plasma concentrations was associated

with prolongation of the PR interval, however, the probability of PR interval ≥200 msec at the clinical dose of 100 mg QD was predicted to be low.

1.2.3.4. Clinical Data

Study B7461001 is a Phase 1/2, dose-escalation, safety, PK, pharmacodynamics, and anticancer efficacy exploration study of lorlatinib as a single-agent in patients with advanced ALK-positive and advanced 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). The Phase 1 portion of the study was designed to estimate the MTD for lorlatinib as a single-agent with advanced ALK-positive or advanced ROS1-positive NSCLC with or without asymptomatic CNS metastases, and to determine recommended Phase 2 dose (RP2D). Enrollment in the Phase 1 part of the study was completed and 54 patients were treated. The Phase 2 portion of the study 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 or with advanced ROS1-positive NSCLC. Enrollment in the Phase 2 part of the study was completed and 275 patients were treated. Additionally, to evaluate the safety and tolerability of lorlatinib in Japanese patients, lead-in cohort (LIC) was to evaluate lorlatinib safety and PK in patients treated at a previously tested dose in Phase 1.

As of the data cutoff date of 15 September 2017, lorlatinib has been administered to a total of 54 patients in Phase 1 across 7 QD doses of 10, 25, 50, 75, 100, 150, and 200 mg and 3 twice-a-day (BID) doses of 35, 75, and 100 mg; and to 275 patients in Phase 2 at 100 mg QD, and to 3 patients at 100 mg in the Japan LIC.

Note, the leading designation included in a Pfizer sponsored lorlatinib study protocol number (ie, “B746”) will be omitted in the text (but not in tables or figures) for simplicity. For example, study protocol number B7461001 will be referred to in the text as Study 1001.

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 the steady-state of lorlatinib, 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.

One (1) DLT was reported in a Phase 1 patient enrolled at the 200 mg QD dose level who received <16 out of 21 planned doses in Cycle 1 due to toxicities attributed to lorlatinib, which met the protocol definition of a DLT. This patient experienced Grade 1 and Grade 2 CNS effects during Cycle 1, including Grade 2 aphasia and cognitive disorder, and Grade 1 visual impairment and abnormal dreams. As a result, lorlatinib was temporarily discontinued and the patient did not receive at least 16 of the planned 21 doses in Cycle 1.

Although the continual reassessment method (CRM) model used in Phase 1 recommended dose escalation above 200 mg QD, the CNS effects observed at this dose and at the 150 mg QD dose were considered intolerable to some patients and the majority had treatment-related AEs resulting in dose interruption and/or dose reduction. As a result, it was agreed upon by the sponsor and the Phase 1 investigators to evaluate doses lower than 200 mg QD and consider an alternative dosing regimen. BID dosing was evaluated to potentially modulate these AEs, but the patients did not tolerate the 75 mg or 100 mg BID dosing.

Overall, 100 mg QD was a well-tolerated dose in Phase 1. Additionally, based on the PK data observed in Phase 1, simulated patient exposure suggested that the 100 mg QD dose was the lowest dose that would exceed the lorlatinib minimum effective concentration (C_{eff}) of 150 ng/mL, to inhibit ALK G1202, during the majority of the 24-hour dosing interval, once steady-state was reached.

Therefore, while the MTD was not formally identified, 100 mg QD was chosen as the RP2D based on the entirety of the safety, efficacy, and clinical pharmacology data.

Safety

Lorlatinib was generally tolerable and, when needed, AEs were manageable through dosing interruption, dose reduction, and/or standard supportive medical therapy.

As of the data cutoff date of 15 September 2017, there were 295 patients in the safety analysis data set received lorlatinib treatment at 100 mg dose, with 143 patients still in treatment. There were also 37 patients in Phase 1 portion received lorlatinib at doses other than the RP2D of 100 mg QD.

The 100-mg Pooled Group of study 1001 includes all patients who received lorlatinib 100 mg QD (RP2D). This group consisted of 17 patients from the Phase 1 portion, 275 patients from the Phase 2 portion, and 3 patients from the Japan Lead-in Cohort (LIC). In total, this group consisted of 295 patients.

In the 100-mg pooled group of study 1001, the most frequent (>20%) treatment-related AEs were hypercholesterolemia (83.7%), hypertriglyceridemia (65.8%), edema (44.4%), peripheral neuropathy (33.6%), cognitive effects (21.7%) and weight increased (20.7%). Grade 3 and Grade 4 treatment-related AEs were reported in 115 (39.0%) and 18 (6.1%) patients, respectively. The most frequently reported (>10%) treatment-related Grade 3 AEs were hypercholesterolemia (14.6%) and hypertriglyceridemia (13.9%). The most frequently reported (>2%) treatment-related Grade 4 AE was hypertriglyceridemia (2.4%).

Twenty-three (23) (7.8%) patients had treatment-related Serious Adverse Events (SAEs). The most frequent (>1 patient) treatment-related SAE was cognitive effects (3 patients, 1.0%). Grade 3 treatment-related SAEs were reported in 4.4% patients and Grade 4 treatment-related SAEs were reported in 1.4% of patients.

Lorlatinib toxicity was generally manageable through temporary discontinuations of dosing with or without dose reduction, as permanent discontinuation due to an AE was not commonly reported in the 100-mg pooled group of Study 1001 (7.8%). Temporary discontinuations of dose, dose reductions, and/or standard medical therapy allowed most patients treated with lorlatinib to remain in the study and continue receiving treatment. Altogether, 22.7% of patients had AEs associated with dose reductions, 31.9% had AEs associated with temporary discontinuations of dose, and 2.7% of patients discontinued lorlatinib in association with treatment-related AEs, in the 100-mg pooled group of Study 1001.

CNS effects could be categorized into 3 different categories including cognitive effects, mood effects and speech effects, which have been reported separately. The treatment related including cognitive effects, mood effects and speech effects have been observed in 21.7%, 15.3%, 8.1% patients in the 100-mg pooled group of Study 1001. The most common treatment related AEs in each category are memory impairment and irritability, slow speech, each occurring in 9.5%, 5.8% and 3.4% 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 Phase 2 study will be limited to mood and suicidality.

Changes in QTc and PR prolongation have also been observed in the study. QT interval prolongation was reported as treatment related AE in 5.4% patients in the 100-mg pooled group of Study 1001. And no Grade 3, Grade 4, Grade 5 treatment related AE have been reported. There were no atrioventricular block events in Phase 1, Grade 1 atrioventricular block was reported in 2 patients in Phase 2 as treatment related AE. No Grade 2 and above treatment related atrioventricular block have been reported. Basing on the preliminary evidence, the assessment of ECG and heart function will be conducted in this Phase 2 study.

In the 100-mg pooled group of Study 1001, 11.3% patients had a maximum decrease from baseline in LVEF ≥20%. The mechanism for the LVEF decreases is currently unclear, and it will need be further explored. Thus, the decrease of LVEF will also be evaluated in this study.

Peripheral neuropathy, mood disorders, cognitive disorders, speech disorders, vision disorders, diarrhoea, constipation, arthralgia, oedema, fatigue, weight increased are identified risks associated with lorlatinib administration, for which dose delay and/or dose reduction have been effective.

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

Efficacy

As of the data cutoff date of 15 March 2017, among the 53 patients who were evaluable for efficacy in Phase 1 as of the data cutoff date, the independently assessed objective response rate (ORR) was 41.5% (95% CI: 28.1, 55.9) and included 1 (1.9%) confirmed complete responses (CR) and 21 (39.6%) confirmed partial responses (PR). Eleven (11 [20.8%]) patients had stable disease (SD) as their best overall response.

Forty-two (42) Phase 1 patients had CNS metastases at study entry. Of the 42 patients evaluable for intracranial response at the time of the data cutoff, 13 (31.0%) patients had an independently confirmed CR and 5 (11.9%) patients had a confirmed PR, resulting in an intracranial ORR of 42.9% (95% CI: 27.7, 59.0). Further, 8 (19.0%) patients had SD as their best overall response.

Among the 274 patients who were evaluable for efficacy in Phase 2 as of the data cutoff date, the independently assessed ORR was 50% (95% CI: 43.9, 56.1) and included 7 (2.6%) confirmed CRs and 130 (47.4%) confirmed PRs. Eighty-two (82 [29.9%]) patients had stable disease (SD) as their best overall response.

One hundred and sixty-five (165) Phase 2 patients had CNS metastases at study entry. Of the 165 patients evaluable for intracranial response at the time of the data cutoff, 48 (29.1%) patients had an independently confirmed CR and 42 (25.5%) patients had a confirmed PR, resulting in an intra-cranial ORR of 54.5% (95% CI: 46.6, 62.3). Further, 49 (29.7%) patients had SD as their best overall response.

Overall Results

Basing on the data from study B7461001, 100 mg QD dose of lorlatinib monotherapy, was chosen as the RP2D, based on the entirety of the safety, efficacy, and clinical pharmacology data. Lorlatinib conferred a clinically meaningful benefit in patients with advanced ALK-positive NSCLC across a range of treatment with prior ALK inhibitors and/or chemotherapies, including in treatment settings such as crizotinib treated or second-generation of ALK inhibitor treated disease. Lorlatinib was generally tolerable, as AEs were primarily mild to moderate in severity, and manageable as rates of permanent discontinuations due to AEs were low and could be managed by dosing interruption, dose reduction, and/or standard supportive medical therapy.

Basing on the result from B7461001 study, FDA granted a breakthrough therapy designation to lorlatinib for patients with ALK-positive metastatic NSCLC who have previously received 1 or more ALK inhibitors in 2016, as well as a priority review to a new drug application (NDA) for lorlatinib in the same indication.

1.2.4. Study Rationale

Since 2013, after receiving approval by China Food and Drug Administration (CFDA) in treatment of ALK-positive advanced NSCLC in China, Xalkori® has become the standard of care for ALK-positive advanced NSCLC patients. Consequently, the treatment resistance to crizotinib becomes common in these patients. Acquired ALK kinase domain mutation and brain metastasis are the two major mechanism of refractory or resistance to crizotinib treatment.[13,14,15]

To fulfill this treatment need in ALK-positive advanced NSCLC patients, second-generation of ALK inhibitors have been developed and showed treatment activity. In the near future, the second generation ALK inhibitors will be increasingly used in both crizotinib resistant and treatment naïve patients, and eventually, the resistance to 2nd gen ALK inhibitor will be more and more common.

The resistance to ALK inhibitors appears much more complex as a greater variety of mutations are found in crizotinib resistant patients. And in ceritinib or alectinib resistant patients, ALK mutation G1202R, V1180L and I1171T have all been observed.

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.[27] Further, lorlatinib appears to be the only ALK TKI active against certain mutations that are the most difficult to inhibit after second-generation ALK inhibitor resistance, such as the G1202R mutation.[25]

Lorlatinib has the potential to improve anti-tumor activity in ALK inhibitor resistance and refractory ALK-positive advanced NSCLC, 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,[25] and able to cross the blood brain barrier. This study will evaluate the antitumor activities of lorlatinib in ALK inhibitor treated patients, which include both crizotinib treated and ALK inhibitors other than crizotinib treated patients.

1.2.5. Rationale for Starting Dosing Regimens

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 in B7461001 study.

Additional information may be found in IB.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Primary Endpoint(s):
• To evaluate the anti-tumor effect of lorlatinib as a single agent as measured by ORR per RECIST v1.1 in locally advanced or metastatic ALK-positive NSCLC patients whose disease has progressed after crizotinib treatment.	• Objective Response (OR) in patients whose disease has progressed after crizotinib (Cohort 1) by independent central radiology (ICR) assessment per RECIST v1.1 (Appendix 3).
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the anti-tumor effect of lorlatinib as a single agent as measured by ORR per RECIST v1.1 in locally advanced or metastatic ALK-positive NSCLC patients whose disease has progressed after ALK inhibitor treatment other than crizotinib.	• OR in patients whose disease has progress after ALK inhibitor treatment other than crizotinib (Cohort 2) as assessed by RECIST v1.1 per ICR assessment.
• To evaluate the PFS and OS in locally advanced or metastatic ALK-positive NSCLC patients whose disease has progressed after crizotinib and other ALK inhibitor treatment, respectively.	• Progression-free survival (PFS) as assessed by RECIST v1.1 per ICR assessment and investigator assessment and Overall survival (OS) in both Cohorts.
• To evaluate other antitumor activities in locally advanced or metastatic ALK-positive NSCLC patients whose disease has progressed after crizotinib and other ALK inhibitor treatment, respectively.	• Intracranial objective response (IC-OR), Duration of response (DoR), Duration of intracranial response (IC-DoR), Time to tumor response (TTR) as assessed by RECIST v1.1 per ICR assessment and investigator assessment in both Cohorts.
• To evaluate the safety and tolerability of lorlatinib treatment in locally advanced or metastatic ALK+ NSCLC patients whose disease has progressed after crizotinib and other ALK inhibitor treatment.	• Safety: AE; laboratory abnormalities; ECG, LVEF, CNS effects.
• To evaluate the pharmacokinetics (PK) of lorlatinib and potential pharmacokinetic (PK) /pharmacodynamics relationship for lorlatinib if appropriate.	• PK: parameters on Day 1 of Cycle 1 and at steady state: C_{max}, T_{max}, AUC_t, AUC_{tau} at steady state, AUC_{inf}, CL/F, Vz/F, $t_{1/2}$ and R_{ac} as data permit.
CCI [redacted]	[redacted]
[redacted]	[redacted]

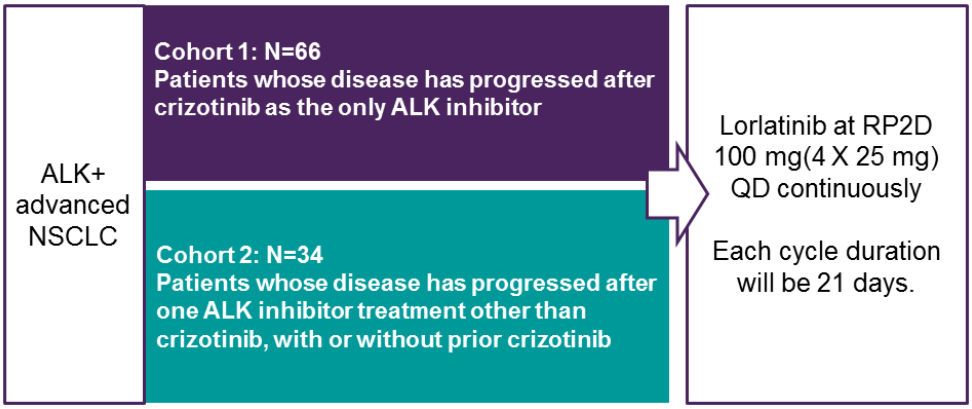
3. STUDY DESIGN

This is a Phase 2, China only, multi-center (at approximately 30 sites), open-label, dual-cohort study, in which approximately 100 ALK-positive locally advanced or metastatic NSCLC patients will be enrolled to receive lorlatinib monotherapy according to the study design shown in Figure 1. The patients should have (also see Section 4.1).

- (in Cohort 1) Disease progression after crizotinib as the only ALK inhibitor. Approximately 66 patients will be enrolled to this cohort.

- (in Cohort 2) Disease progression after one ALK inhibitor other than crizotinib. Approximately 34 patients will be enrolled to this cohort.

Figure 1. Study B7461024 Design



A cycle duration will be 3 weeks (**21 days)** and will always be considered 3 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 ICR, subject refusal, subject lost to follow-up, unacceptable toxicity, or the study is terminated by the sponsor, whichever comes first (see Section 6.4 Subject Withdrawal).

Subjects who develop radiological disease progression confirmed by ICR 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 ICR 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 subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol.

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

4.1. Inclusion Criteria

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

1. Evidence of histologically or cytologically confirmed diagnosis of locally advanced or metastatic ALK-positive NSCLC where ALK status has been previously established by the Ventana ALK (D5F3) CDx Assay (Roche Diagnostics), the Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular), or the EML4-ALK Fusion Gene Detection Kit (AmoyDx).

2. Subject should have:

   a. (in Cohort 1) Disease progression after crizotinib as the only ALK inhibitor;

   b. (in Cohort 2) Disease progression after one ALK inhibitor other than crizotinib, with or without prior crizotinib.

3. Prior treatment with an ALK inhibitor must have completed ≥5 half-lives prior to study entry.

4. All Subjects must have at least 1 measurable extracranial target lesion according to RECIST v1.1 that has not been previously irradiated. CNS metastases are allowed if:

   a. Asymptomatic: either not currently requiring corticosteroid treatment, or on a stable or decreasing dose of ≤10 mg QD prednisone or equivalent; or

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

5. Eastern Cooperative Oncology Group performance status (ECOG PS) 0, 1, or 2.

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

7. Adequate bone marrow functions:

   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.

8. Adequate pancreatic function:

    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 subject may be enrolled.

9. Adequate renal function:

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

10. Adequate liver function:

    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).

11. Acute effects of prior radiotherapy and chemotherapy resolved to baseline severity or to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 except for AEs that in the investigator's judgment do not constitute a safety risk for the subject.

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

    a. 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;

    b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

    c. Have medically confirmed ovarian failure.

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

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

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

4.2. Exclusion Criteria

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

1. More than 1 prior chemotherapy regimen prior to enrollment in advanced/metastatic setting.

   If disease recurred/relapsed within the adjuvant chemotherapy treatment or ≤ 6 months after the completion of the adjuvant chemotherapy, then the adjuvant chemotherapy is considered as the first line systemic chemotherapy to the disease.

2. Systemic anti-cancer therapy completed within a minimum of 5 half-lives of study enrollment.

3. Prior therapy with an antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways, including, but not limited to, anti-programmed cell death protein 1 (anti-PD-1), anti- programmed cell death protein ligand 1 (anti-PD-L1), anti-PD-L2, anti-cluster of differentiation 137 (anti-CD137), or anti-cytotoxic T lymphocyte associated antigen 4 (anti-CTLA-4) antibody.

4. Known epidermal growth factor receptor (EGFR) activating mutations; known prior therapy with EGFR TKI(s) (the prior treatment with brigatinib is allowed as an ALK TKI).

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

6. Radiation therapy within 2 weeks prior to enrollment. Palliative radiation must have been completed at least 48 hours prior to enrollment. Stereotactic or partial brain irradiation must have completed at least 2 weeks prior to enrollment. Whole brain irradiation must have completed at least 4 weeks prior to enrollment.

7. Spinal cord compression unless the subject has good pain control attained through therapy, and there is complete recovery of neurological function for the 4 weeks prior to enrollment.

8. 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.

9. Known prior or suspected severe hypersensitivity to lorlatinib or any component in the formulation; known prior therapy with lorlatinib.

10. Active and clinically significant bacterial, fungal, or viral infection including hepatitis B virus (HBV), hepatitis C virus (HCV), known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

11. Clinically significant cardiovascular disease (both arterial and venous) and non-vascular cardiac conditions, (active or within 3 months prior to enrollment, which may include, but not are 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;

    - Nonvascular cardiac disease such as congestive heart failure (New York Heart Association Classification Class ≥ II), second- degree or third-degree atrioventricular block (unless paced) or any AV block with PR interval >220 msec; or

    - Ongoing cardiac dysrhythmias of CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 bpm (unless subject is otherwise healthy such as long-distance runners, etc.), machine-read electrocardiogram (ECG) with QTc >470 msec, or congenital long QT syndrome.

12. Subject with predisposing characteristics for acute pancreatitis according to investigator judgment, including but not limited to uncontrolled hyperglycemia, current gallstone disease, in the last month prior to enrollment.

13. 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.

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

15. 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 administration of lorlatinib:

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

16. 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 and/or the sponsor, would make the subject inappropriate for entry into this study.

17. Subject 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 subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

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

19. Pregnant female subjects; breastfeeding female subjects; fertile male subjects and female subjects 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 21 days if female, after the last dose of investigational product.

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. 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 patient has selected a highly effective method of contraception for the individual patient and his or her partner(s) from the permitted list of contraception methods (see below) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the schedule of activities, the investigator or designee will inform the patient 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 patient's chart (patients need to affirm their consistent and correct use of at least one of the appropriate methods of contraception).

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

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 21 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).

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-and continuing for at least 97 days after the last dose of lorlatinib.

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 patients 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 methods 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, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject 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 subject'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 subject directly, and if a subject 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 product(s) is lorlatinib (PF-06463922).

5.1. Allocation to Treatment

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

A subject must sign an informed consent document (ICD) before being evaluated for study entry. Once a subject who has met inclusion and exclusion criteria has provided a signed ICD, allocation of subjects to lorlatinib treatment 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 subject 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.

Qualified subjects will be enrolled to the study to receive lorlatinib monotherapy at the RP2D of 100 mg QD, administered as 4×25 mg oral tablets, continuously. Study treatment should be initiated preferably on the randomization day but no later than 1 day after randomization.

5.2. Subject Compliance

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

A patient diary will be provided to the subjects to aid in lorlatinib compliance. The diary will be maintained by the subject to include unchanged, missed, or changed doses.

Subject will be required to return to the investigational site all bottles of lorlatinib at the end of each 21-day cycle during the planned visit at the site. The number of lorlatinib tablets remaining will be documented and recorded at each clinic visit.

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

5.3. Investigational Product Supplies

5.3.1. Dosage Form(s) and Packaging

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.

5.3.2. 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.

Lorlatinib will be dispensed at the beginning of every 21-day cycle (or as otherwise indicated) using an IRT drug management system. Subjects 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 subjects clearly understand the directions for self-medication. Subjects should be given sufficient supply to last until their next study visit. Subjects 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.

5.4. Administration

All study treatments will be administered on an outpatient basis.

A cycle is defined as 21 days, irrespective of any dose delays/dosing interruptions or missed doses which may affect nominal days of each cycle.

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. Subjects will swallow the investigational product whole, and will not manipulate or chew the investigational product prior to swallowing. A dosing card will be provided to the subjects to provide guidance for the correct use of lorlatinib. Subjects 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 subject 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).

On PK sampling days, the lorlatinib dose should be taken in the clinic under the supervision of the study site personnel. The lorlatinib dose should be administered after the 0 hour (predose) PK sample has been collected.

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

5.4.1. Treatment duration

The study treatment may continue until disease progression confirmed by independent central radiology (ICR) review, unacceptable toxicity, subject lost to follow-up, or subject refusal, or the study is terminated by the sponsor, whichever comes first.

If the subject has documented PD by ICR, subjects should be discontinued from study treatment. However, if according to the investigator's clinical judgment and after discussion between the investigator and Pfizer, if a subject with evidence of PD is still experiencing clinical benefit, the subject may be eligible for continued lorlatinib treatment. The investigator's judgment should be based on the overall benefit/risk assessment and the subject's clinical condition, including ECOG performance status, clinical symptoms, adverse events and laboratory data.

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. Subjects are to be instructed to notify their investigators at the first occurrence of any adverse event.

If a dosing interruption longer than 4 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 subject may resume treatment after a lapse of greater than 4 weeks.

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. Subjects will be monitored closely for toxicity, and the dose of lorlatinib may be adjusted as indicated in Table 1 below. All dose modifications will be reported in the Case Report Form (CRF).

Table 1. Lorlatinib Dose Levels for Intrapatient 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.	

Intrapatient 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). It is recommended that in case of lorlatinib dose decrease, the subject is assigned new drug rather than using less tablets from the bottle assigned at previous visit.

If a subject has a significant toxicity from lorlatinib treatment which fails to recover within 28 days (4 weeks) or, in the opinion of the investigator, requires permanent discontinuation of the treatment based on the severity of the adverse event, then this subject should not be further treated with lorlatinib but should remain in the study with ongoing tumor assessments until RECIST-defined disease progression by the ICR.

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.

Table 2. Lorlatinib Dose Modifications for Lorlatinib-Related Toxicities

Toxicity	Grade 1**	Grade 2**	Grade 3	Grade 4
Non-Hematologic Toxicities				
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

Table 2. Lorlatinib Dose Modifications for Lorlatinib-Related Toxicities

Toxicity	Grade 1**	Grade 2**	Grade 3	Grade 4
Pneumonitis (in the absence of disease progression, pulmonary embolism, positive cultures or radiation effect) section	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 5.5.2)	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

Table 2. Lorlatinib Dose Modifications for Lorlatinib-Related Toxicities

Toxicity	Grade 1**	Grade 2**	Grade 3	Grade 4
* Subjects 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. ** 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. Section If a subject has a potential diagnosis of pneumonitis or drug-related lung injury the same evaluations/procedures provided in Section 5.5.3 should be considered to assist or exclude the diagnosis of pneumonitis during this period.				
Hematologic Toxicities				
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 the same dose; otherwise, withhold dose until toxicity is Grade ≤1 (or baseline) then rechallenge at the same dose or reduce by 1 level

Table 2. Lorlatinib Dose Modifications for Lorlatinib-Related Toxicities

Toxicity	Grade 1**	Grade 2**	Grade 3	Grade 4
Lipid Elevation Toxicities[α]				
Cholesterol	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. Continue lorlatinib at the same dose without interruption	Increase the dose of the statin or other lipid-lowering agent, or change to a new statin/lipid lowering agent. Withhold lorlatinib dose until toxicity is Grade ≤2 Re-challenge at same dose while maximizing lipid lowering therapy in accordance with respective prescribing information If ≥ Grade 3 hypercholesterolaemia recurs despite maximal lipid lowering therapy in accordance with respective prescribing information, reduce lorlatinib by 1 dose level
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. Continue lorlatinib at the same dose without interruption	Increase the dose of the statin or other lipid-lowering agent, or change to a new statin/lipid lowering agent. Withhold lorlatinib dose until toxicity is Grade ≤2 Re-challenge at same dose while maximizing lipid lowering therapy in accordance with respective prescribing information If ≥ Grade 3 hypertriglyceridaemia recurs despite maximal lipid lowering therapy in accordance with respective prescribing information, reduce lorlatinib by 1 dose level

Table 2. Lorlatinib Dose Modifications for Lorlatinib-Related Toxicities

Toxicity	Grade 1**	Grade 2**	Grade 3	Grade 4
[α] See also instructions provided in Section 5.5.1 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. Then resume at the same dose or reduce by 1 dose level	Withhold dose until toxicity is less than or equal to Grade 1. Then resume at 1 reduced dose level	Withhold dose until toxicity is less than or equal to Grade 1. Then resume at 1 reduced dose level	Permanently discontinue lorlatinib
[β] Examples of CNS effects could include changes in speech, memory, sleep, cognition, or vision.				

5.5.1. 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.

5.5.2. PR Interval Prolongation

Analysis of ECG data from ongoing and completed human studies with lorlatinib has identified a subset of subjects 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	No symptomatic	Symptomatic
1st-Degree Heart Block (PR interval >200 msec)	**No dose hold or reduction needed.** Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely	**Withhold dose.** Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If symptoms resolve, resume at same dose or at 1 reduced dose level
2nd-Degree Heart Block	**Withhold dose.** Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If subsequent ECG does not show second degree block, resume at same dose or 1 reduced dose level	**Withhold dose.** Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic AV block persists. If symptoms and the second degree block resolve or if subjects revert to asymptomatic first degree AV block, resume at 1 reduced dose level
Complete Heart Block	**Withhold dose.** Assess concomitant medications and electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Temporary pacemaker placement may be indicated for severe symptoms associated with AV block. If AV block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, may resume at full dose. If no pacemaker placed, resume at 1 reduced dose level only when symptoms resolve AND PR interval is less than 200 msec.	

5.5.3. Pneumonitis/Pneumonia

Investigators must evaluate thoroughly subjects who demonstrate potential signs/symptoms of pneumonitis/pneumonia. If a subject 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 subjects. Consider appropriate serologies (mycoplasma, legionella, cytomegalovirus, other viruses, etc).
- Thoracentesis if pleural fluid is present (culture, microbiology, cytology).

- Bronchoscopy with bronchoalveolar lavage if appropriate. The bronchoalveolar lavage 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.

- For *Asian countries based subjects*, 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.

5.6. Management of Overdose

An overdose is defined as any dose of lorlatinib >100 mg QD. Any overdose must be recorded in the study drug section of the CRF. If an extra dose is taken during a day, the next dose should not be taken.

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 are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels. Any storage conditions stated in the SRSD 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.

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

5.8. Investigational Product Accountability

The investigator 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 study drug must be returned to the investigator by the subject at the end of each cycle and at the end of the study. 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 investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.9. Concomitant Treatment(s)

Concomitant treatment considered necessary for the subject'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 receptor activator of nuclear factor kappa-B (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.

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 subject 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. 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 lorlatinib is permanently discontinued. 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 (NTI) may have increased effect. The concurrent use of drugs which are NTI P-gp substrates, 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.

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

No additional concurrent anti-tumor treatment will be permitted while subjects are receiving study treatment, which includes but not limited to anti-cancer systemic chemotherapy and biological therapy.

5.9.3. Other 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 Section 5.9.6).
- 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.[30] Subjects who enter the study on stable doses of erythropoietin or darbepoetin may continue this treatment, and subjects may start either drug during the study at the discretion of the investigator.

5.9.5. Concomitant Surgery

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

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

5.9.6. Concomitant Radiotherapy

Radiation therapy during the treatment phase is not allowed, with the exception described as below.

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.

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 predefined windows outlined in this protocol.

6.1. Screening

Informed Consent must be obtained prior to undergoing any study specific procedures.

CCI [redacted]

For screening procedures see the SCHEDULE OF ACTIVITIES and ASSESSMENTS section.

6.1.1. Determination of ALK Status

Evidence of positive ALK status as previously determined through use of the Ventana ALK (D5F3) CDx Assay (Roche Diagnostics), the Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular), or the EML4-ALK Fusion Gene Detection Kit (AmoyDx), must be available at screening stage before enrollment.

CCI [redacted]

CCI [redacted]

[redacted]

- [redacted]
- [redacted]

CCI

[redacted]

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. Subject Withdrawal

Subjects 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 Withdrawal From the Study Due to Adverse Events section) or behavioral reasons, or the inability of the subject 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. However, subjects with disease progression who are continuing to derive clinical benefit from the study treatment per the investigator will be eligible to continue with lorlatinib 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 permanent discontinuation per the investigator's judgement;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to follow-up;
- Subject refused further treatment (follow up permitted by subject);

- 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 Visit

For survival follow up procedures see SCHEDULE OF ACTIVITIES table and ASSESSMENTS section.

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

If the subject refuses further visits, the subject should continue to be followed for survival unless the subject withdraws from the study, and also withdraws consent for disclosure of future information.

If the subject 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 subject. 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.

Available results for assessments that have been performed prior to informed consent being obtained as part of the patient's on-going routine standard of care testing (laboratory tests or tumor imaging scans) may be used to satisfy patient eligibility assessment, provided they have been performed within the required timing (that is 7 days prior enrollment for laboratory tests or 28 days prior enrollment for tumor imaging or 6 weeks prior enrollment for bone scan [or bone MRI if preferred by investigator]) and meet the related criteria.

End of treatment (EOT) visit should be performed no later than 4 weeks (+1w) from the last dose of investigational product or when decision taken to provide alternative anti-cancer therapy, whichever is sooner.

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 need to include all known or suspected disease sites. Imaging to include chest, abdomen, and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans (contrast enhanced CT/MRI is preferred unless contraindicated). Brain MRI (Gadolinium contrast enhanced) or brain CT (contrast enhanced) to be used for assessment of CNS lesions (even if brain metastases not suspected), with contingent slices of 1 mm for lesions 5 mm – 10 mm in size, 5 mm for lesions greater than 10 mm (target intracranial lesions need to be suitable for accurate measurements with a minimum size of 5 mm by MRI or CT or no less than double the slice thickness, whichever is largest). CNS imaging using MRI/CT (contrast enhanced is preferred unless contraindicated) is required at baseline in all patients and at every tumor assessment. Bone scans (or bone MRI if preferred by investigator) to be performed at baseline for all subjects and repeated every 18 ±1 weeks on study only if evidence of bone metastases is observed at baseline.

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. 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, assessed by a modified version of RECIST v1.1 (Appendix 3).

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 6 weeks ±1 week starting from the first dose of the investigational product while on treatment and during post-treatment follow-up period, until documented progression of disease by ICR; During post-treatment follow-up period, if applicable, bone scan (or bone MRI if preferred by investigator) to be performed every 18 weeks ±1 week until documented progression of disease by ICR. The responses will have to be confirmed ≥4 weeks after the initial response is observed. If the disease progression is suspected during the study, an unscheduled tumor assessment may be conducted before the regular tumor assessment visit, if applicable.

Tumor assessment should be repeated at the end of treatment (EOT) visit if more than 6 weeks have passed since the last evaluation. Tumor assessments must continue until documented progression of disease by ICR. Subjects who discontinue treatment without PD should be followed until PD confirmed by ICR, regardless of subsequent anti-cancer treatments. For subjects continue lorlatinib treatment after disease progression by ICR (based on the investigator's judgement of clinical benefit in spite of confirmed disease progression), tumor assessment is in need when clinically indicated.

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,[31] see Appendix 3.

All subjects' files and radiologic images must be available for independent central radiology review. Instructions for submission of these images will be provided in the Study Reference Manual. Specific imaging sequences, step-by-step and storage of images will be defined in a separate Imaging Charter developed by the imaging vendor.

Management of incidental findings

An incidental finding is one unknown to the subject that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study, but is unrelated to the purpose and beyond the aims of the study.

Radiologic images will be reviewed by a central review facility. The purpose of this review is to evaluate images for tumor response assessment. Central image review is not a complete medical review of the subject and no incidental findings will be shared with the principal investigator, site staff, or the subject. All safety reviews will be the sole responsibility of site staff.

7.2. Expedited Independent Central Review of Disease Progression

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

7.3. Pregnancy Testing

For female subjects of childbearing potential, a serum or urine pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, 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 lorlatinib treatment. Following a negative pregnancy test result at screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit before the subject may receive lorlatinib treatment. Pregnancy tests will be 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. Additional pregnancy tests may also be undertaken if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject 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/multigated acquisition (MUGA), laboratory assessments, including pregnancy tests and verification of concomitant treatments. 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.

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.

7.4.3. Vital Signs and Physical Examinations

Subjects will have a physical examination to include major body systems, body weight, blood pressure, pulse rate, body temperature, assessment of ECOG performance status, and height (height will be measured at screening only) at the time points described in the SOA. Blood pressure and pulse rate should be taken with the subject in the seated position after the subject 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 electrocardiograms (ECG) assessments, except for ECG at Day 1 of Cycle ≥3, which will be single readings according to Schedule of Activities.

All subjects 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 (triplicates) will be performed approximately 2 minutes apart (or within 10 minutes, whichever is appropriate) to determine PR interval and mean QTc (average of triplicates). The ECG must occur prior to any blood sample collections or venipuncturing if conducted on the same day, except for the specific requirement in the protocol (SOA & Section 7.5).

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 subject 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 subject experiences PR interval prolongation >200 msec or second-degree or third-degree AV block, while on treatment with lorlatinib, refer to Section 5.5.2.

If subject 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. Additional triplicate ECGs may be performed as clinically indicated and relevant results reported in the CRF as ‘unplanned visits’ if applicable.

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. Assessment of Mood

An assessment of mood will be administered to subjects 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 subjects 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).

7.4.7. Assessment of Suicidal Ideation and Behavior

To assess suicidal ideation behaviors, the Columbia Suicide Severity Rating Scale (C-SSRS)[32] will be administered to subjects 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.

For C-SSRS rating assessments, only qualified raters will be allowed to evaluate and/or rate subjects in this study. The minimum qualifications a rater must meet for this assessment is:

- Educational level: Medical Doctor or Registered Nurse.
- Prior clinical experience: at least 1 year experience with clinical trial.
- Prior scale experience: Prior training with C-SSRS within the past two years with valid documented certification will exempt rater from having to retake C-SSRS training. Upon 2 year expiration of documented certification, raters will be required either to retake C-SSRS training or resubmit valid, current documented certification. Should the two years lapse during the course of the study, retraining updated training and a renewed certificate will be required.

Proposed raters who do not meet specific criteria but who may be qualified based on unique circumstances may be individually reviewed by the study clinical team to determine whether or not a waiver may be issued. The rater must become certified to perform selected study assessments before he or she can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written and signed documentation will be provided by the site for each rater's certification. In return, each site will be provided written and signed documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staffs who administer ratings will be verified in the site study documentation during the conduct of the study.

7.5. Pharmacokinetics Assessments

All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within 10% of the nominal time (eg, within 6 minutes of a 60-minute sample) from dosing will not be captured as a protocol deviation, as long as the exact time of the sample collection is noted on the source document and the data collection tool (eg, CRF). During the study, actual collection times may change but the number of samples will remain the same.

Plasma samples will be assayed for lorlatinib using a validated analytical method(s) in compliance with Pfizer standard operating procedures. Details regarding the storage and shipping of plasma samples will be provided in the Study Manual.

As part of understanding the pharmacokinetics of the study drug, samples may be used for potential qualitative and/or quantitative metabolite analyses and/or evaluation of the bioanalytical methods for lorlatinib and its metabolites (if possible). The results of such analyses may not be included in the clinical report.

Plasma samples for determination of plasma concentrations of lorlatinib will be collected at time 0 (pre-dose), and any time between 1 to 2 hours after the lorlatinib dose on Days 1 of Cycle 2 to 5 in all subjects. In order to obtain 12 evaluable full PK profiles, in up to 16 subjects, Plasma samples will be collected at time 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 9, and 24 hours on Day 1 and Day 15 of Cycle 1. Note: 1) When collecting the serial PK sample at 8 hour and 9 hour, if the actual collection time of the 8 hour sample is nearing the 9 hour nominal time (within the 10% window of the 9 hour collection time), the 9 hour sample should still be collected after the 8 hour sample and as close to the 9 hour nominal time as possible. 2) In the event of any dose interruption in 15 day time period prior to Day 15 of Cycle 1, the planned intensive PK sampling schedule on C1D15 is suggested to be extended to the Day 1 of next cycle.

Additional plasma samples may be requested from subjects experiencing unexpected or serious adverse events.

During all study periods, blood samples (about 3.0 mL) to provide approximately 1.2 mL plasma for pharmacokinetic analysis of lorlatinib will be collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) at times specified in the Section 6 of the protocol.

Lorlatinib is light sensitive; all steps must be performed out of direct light. It should be noted that once collected, samples should be processed immediately and kept out of direct light due to the light sensitive nature of lorlatinib. Once frozen, samples must not thaw, including during shipment.

- Details regarding the collection, processing, storage and shipping of the blood samples will be provided in the laboratory manual.

- Lorlatinib plasma samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

- The PK samples must be processed and shipped as indicated to maintain sample integrity. Any deviations from the PK processing steps, including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised. Any sample deemed outside of established stability, or of questionable integrity, will be considered a protocol deviation.

The shipment address and assay laboratory contact information will be provided to the investigator site prior to initiation of the study.

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

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 subject/legally acceptable representative. In addition, each study subject/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 (see also the Subject Withdrawal section)

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 subject begins from the time the subject provides informed consent, which is obtained before the subject'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 subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject 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 subject 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 subject 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. 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 test (LFT) abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

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

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.

9.1. Sample Size Determination

The primary objective of the study is to evaluate the anti-tumor effect of lorlatinib as a single agent as measured by ORR per RECIST v1.1 in locally advanced or metastatic ALK-positive NSCLC patients whose disease has progressed after crizotinib treatment, ie, Cohort 1.

As of the original version date of protocol, given there's no ALK inhibitor other than crizotinib approved in China currently, chemotherapy is still considered as standard of care for patients progressed after crizotinib. Based on the current reported results, the ORR of chemotherapy in previous systemic treatment treated patients ranged from 6.9% - 20%.[21,28,29] The ORR was 26.7% even for treatment naive patients.[22] Therefore, ORR of 30% was chosen as the historical control for Cohort 1. The Fleming single stage design will be used to test the null hypothesis (H0) as of ORR ≤30% with 1-sided 0.025 significance level. Assuming at least a 20% increase of ORR with lorlatinib treatment, 66 patients will be required to provide 90% power to reject the null hypothesis. Exact test will be performed at the time of the analysis. If at least 28 responses are observed among the 66 patients enrolled, then the null hypothesis will be rejected, and it will be concluded that the study has demonstrated that the true ORR exceeds 30%. However, at the time of the analysis, the testing will depend on the exact number of patients enrolled.

Cohort 2 will explore the safety and efficacy of lorlatinib in patients with locally advanced or metastasis ALK-positive NSCLC whose disease have progressed after one ALK inhibitor treatment other than crizotinib. As of the original version date of protocol, there was no approved ALK inhibitor other than crizotinib in China, therefore, the eligible patients were very limited and no established standard of care was available. Considering this limitation, Cohort 2 will be exploratory with about 34 patients planned to be enrolled. No specific statistical hypothesis will be tested. Descriptive analyses will be provided for the endpoints.

The sample size of 34 patients will provide the estimated ORR with a maximum width of the 95% CI of 35%, observed with 17 responses out of 34 patients. In order to collect more information of anti-tumor activity, if the patients received study treatment but without adequate baseline tumor assessment or without post baseline tumor assessments, additional patients may be allowed to be enrolled.

With approximately 66 and approximately 34 in Cohort 1 and 2 respectively, this study will provide adequate sample size for safety evaluation with a minimal number of 100.

9.2. Analysis Sets

- Full Analysis Set:

  The full analysis (FA) set will include all subjects who are enrolled, regardless of whether or not treatment was received.

- Per protocol (PP) analysis set:

  The per protocol analysis set will include all enrolled subjects with ALK positive NSCLC, received a prior ALK inhibitor as protocol required, and who received at least 1 dose of lorlatinib:

  - In Cohort 1, received crizotinib as the only ALK inhibitor.
  - In Cohort 2, received one ALK inhibitor other than crizotinib, with or without prior crizotinib treatment.

- Safety Analysis (SA) Set:

  The safety analysis set includes all enrolled subjects who receive at least one dose of lorlatinib.

- PK Analysis Set:

  The PK parameter analysis population is defined as all enrolled subjects who receive at least one dose of study medication and have sufficient information to estimate at least 1 of the PK parameters of interest.

[redacted]

9.3. Efficacy Analysis

All efficacy analyses will be performed by Cohort on the SA set.

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

9.3.1. Analysis of the Primary Endpoint

The primary endpoint is Objective Response (OR) in Cohort 1 per RECIST version 1.1. OR is defined as a complete response (CR) or partial response (PR) recorded from enrollment 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 subject will be considered to have achieved an OR if the subject has a sustained CR or PR according to RECIST version 1.1 definitions. Otherwise, the subject will be considered as a non-responder in the objective response rate (ORR) analysis. Additionally, subjects 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 is defined as the percent of subjects with confirmed OR (CR or PR) relative to the SA set. The corresponding exact 2-sided 95% CI will be provided. The exact test will be performed to test the null hypothesis H0: ORR $\leq$30%. One-sided p-value will be provided.

Sensitivity analyses will be conducted calculating the same ORRs relative to the FA set and PP set, if applicable.

9.3.2. Analysis of Secondary Endpoints

- OR in Cohort 2: The estimated ORR and corresponding exact 2-sided 95% CI will be provided.

- Intracranial objective response (IC-OR): IC-OR is defined the same as OR, but limited to Intra Cranial lesions only on subjects with CNS metastases (ie, Best Overall Intracranial Response as confirmed CR or confirmed PR considering only the lesions having disease site as Brain). Intracranial ORR is defined as the percent of subjects with IC-OR relative to subjects with brain lesions at study entry in the SA set. The estimated IC-ORR and corresponding exact 2-sided 95% CI will be provided.

- Duration of Response (DoR):

  DoR is defined as the time from the first documentation of CR or PR to the first documentation of disease progression or death due to any cause, whichever occurs first.

DoR will only be calculated for the subgroup of subjects with a confirmed objective tumor response. DoR will be summarized in this subgroup using Kaplan-Meier methods and will be displayed graphically where appropriate. The median event time (if applicable) and 2-sided 95% CI for the median will be provided. If the number of subjects with a confirmed CR or PR is small and the use of Kaplan-Meier methods may be limited, the DoR will be listed.

The above analyses will be repeated also for the IC-DoR in the subgroup of subjects with IC-OR.

- Time to Tumor Response (TTR):

  TTR is defined as the time from first dose to first documentation of objective tumor response (CR or PR). TTR will only be summarized for the subgroup of subjects with an objective response. Descriptive statistics mean, median and range will be provided.

- Progression-free Survival (PFS):

  PFS is defined as the time from first dose to first documentation of objective disease progression or to death due to any cause, whichever comes first.

  PFS will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. The median event time (if applicable) and 2-sided 95% CI for the median will be reported.

- Overall Survival (OS)

  OS is defined as the time from first dose to the date of death due to any cause.

  OS will be summarized using the Kaplan-Meier method and displayed graphically where appropriate. The median OS (if applicable) and 2-sided 95% CI for the median will be reported.

9.4. Analysis of Other Endpoints

9.4.1. Analysis of Pharmacokinetics

Plasma pharmacokinetic parameters of lorlatinib on day 1 of cycle 1 (C1D1) and at steady state including the maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration versus time profile from time 0 to time t (AUC_t) and area under the plasma concentration versus time profile within a dose interval (AUC_{tau}) for lorlatinib will be estimated using non-compartmental analysis. If data permit or if considered appropriate, area under the plasma concentration versus time curve to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), oral plasma clearance (CL/F), apparent volume of distribution (V_z/F) and accumulation ratio (R_{ac}) will be also estimated. The C1D1 and steady-state PK parameters will be summarized descriptively by cycle and day.

For lorlatinib, concentrations will be summarized descriptively (n, mean, standard deviation, CV (coefficient of variation), median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, day and nominal time. Individual subject and median profiles of the concentration-time data will be plotted by cycle and day (C1D1 and steady-state) using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

The observed accumulation ratio will be summarized descriptively. Each will be analyzed after natural log transformation using a one-way analysis of variance with a single term for dose. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CIs for the accumulation ratio.

Trough concentrations will be plotted using a box-whisker plot by cycle and day within cycle in order to assess the attainment and maintaining of steady-state.

9.4.2. Pharmacokinetic and Exposure-Response Analysis

Pharmacokinetic and pharmacodynamics data from this study may be analyzed using compartmental or mixed-effect modeling approaches and may also be pooled with other study results. PK/pharmacodynamics modeling may be attempted to investigate any causal relationship between lorlatinib exposure and efficacy, CCI [redacted] or significant safety endpoints. The results of these analyses, if performed, will be reported separately.

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 Cohort and Total.

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 focus of AE summaries will be on Treatment Emergent Adverse Events (TEAE), those with initial onset or increasing in severity after the first dose of study medication. TEAE will be summarized by worst NCI CTCAE v4.03 severity grade and relatedness to study treatment corresponding to system organ class and MedDRA preferred term. The number and frequency of subjects who experienced any AE, serious AE (SAE), treatment-related AE and treatment-related SAE will be reported.

Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE v4.03 Grade ≥3, study drug-related events, and serious adverse events will be considered with special attention.

Detailed information collected for each adverse event will be listed with 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 subjects 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 subjects with MUGA scans or echocardiograms, individual LVEF proportion (%) and its changes from baseline will be summarized by time point. The number of subjects and the percentage whose maximum relative decrease from baseline in LVEF is greater than 20% will be calculated. The number and percentage for subjects whose LVEF proportion falls below lower limit of normal (LLN) and/or maximum relative decrease from baseline is greater than 10% will also be summarized.

9.6. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating pharmacokinetic (PK)/pharmacodynamic modeling, and/or to support clinical development.

9.7. Data Monitoring Committee

This study will not use a data monitoring committee.

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 investigator(s) 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 investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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 subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator shall ensure that the CRFs are securely stored at the study site in encrypted electronic and paper form and will be password protected or secured in a locked room to prevent access by unauthorized third parties.

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

In most cases, the source documents are the hospital or the physician subject 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 subjects (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. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

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

12.3. Subject Information and Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of subject personal data. Such measures will include omitting subject names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable law.

The personal data will be stored at the study site in encrypted electronic and paper form and will be password protected or secured in a locked room to ensure that only authorized study staffs have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, subject names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, subject-specific code. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with the Clinical Study Agreement and applicable privacy laws.

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

Whenever consent is obtained from a subject's legally acceptable representative, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject'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 subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject'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 subject or the subject's legally acceptable representative, before any study-specific activity is performed. The investigator will retain the original of each subject'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 STUDY

End of study is defined as last subject last visit (LSLV).

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 subjects and the hospital pharmacy (if applicable) within one 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 prespecified protocol or was terminated.

EudraCT

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

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report 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.

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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 Elimination
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	Absolute neutrophils count
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand 1
AIDS	acquired immunodeficiency syndrome
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUCinf	area under the plasma concentration versus time curve to infinity
AUCt	area under the plasma concentration versus time profile from time 0 to time t
AUCtau	area under the plasma concentration versus time profile within a dose interval
BBB	blood brain barrier
CCI	[redacted]
BID	bis in die (twice daily)
BNP	B-type natriuretic peptide
C1D1	cycle 1, day 1
CDx	Companion Diagnostics
C_{max}	maximum plasma concentration
C_{trough}	trough plasma concentration
CBR	Clinical Benefit Response
CD	cluster of differentiation
CDS	Core data sheet
Ceff	effective concentration
CFDA	China Food and Drug Administration
CCI	[redacted]
CI	confidence interval
CK	creatine kinase
CL/F	oral plasma clearance
CCI	[redacted]
CNS	central nervous system
CR	Complete response
CRF	case report form
CRM	continual reassessment method
CSA	clinical study agreement

Abbreviation	Term
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	clinical study report
CT	Computed tomography
CTA	clinical trial application
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte associated antigen 4
CV	Coefficient of variation
CYP	cytochromes P450
DDI	Drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	data monitoring committee
CCI	[redacted]
DoR	duration of response
DU	dispensable unit
E-R	exposure response
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EDTA	edetic acid (ethylenediaminetetraacetic acid)
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EML4	echinoderm microtubule-associated protein-like 4
EOT	end of treatment
EU	European Union
EudraCT	European Clinical Trials Database
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
H0	null hypothesis
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	High Density Polyethylene
HIV	human immunodeficiency virus
HDL	high density lipoprotein
hPXR	human pregnane X receptor
HR	hazard ratio
HRQL	health-related quality of life

Abbreviation	Term
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC-DoR	Duration of Intracranial Response
ICF	Informed consent form
ICH	International Conference on Harmonisation
IC-OR	Intracranial Objective Response
IC-ORR	Intracranial Objective Response Rate
ICD	informed consent document
ICR	Independent Central Radiology
ID	identification
CCI	[redacted]
ILD	interstitial lung disease
IND	investigational new drug application
INR	international normalized ratio
IP	investigational product
IRB	institutional review board
IRC	internal review committee
IRT	interactive response technology
IUD	intrauterine device
IWR	interactive web response
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
KRAS	Kirsten rat sarcoma virus
LDL	low density protein
LFT	liver function test
LIC	lead-in cohort
LLN	lower limit of normal
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
MedDRA	medical dictionary for regulatory activities
MDZ	midazolam
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
N/A	not applicable
NCI	National Cancer Institute
NDA	new drug application
NGS	next generation sequencing
NSCLC	non-small cell lung cancer
NTI	narrow therapeutic index
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PCD	primary completion date

Abbreviation	Term
PD	Progression Disease
PE	physical examination
PFS	Progression-Free Survival
P-gp	Permeability glycoprotein
PI	principal investigator
PK	pharmacokinetic
PP	per protocol
PR	Partial response
PRO	Patient-Reported Outcome
PT	prothrombin time
QD	quaque die (every day)
QTc	Corrected QT Interval
R_{ac}	accumulation ratio
RANK	receptor activator of nuclear factor kappa-B
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
ROS1	ROS proto-oncogene 1
RP2D	recommended phase 2 dose
SA	safety analysis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	Stable disease
SIB	suicidal ideation and behavior
SOA	Schedule of Activities
SOC	Standard of care
SOP	standard operating procedure
SRSD	single reference safety document
t1/2	half-life
TBili	total bilirubin
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
T_{max}	time to reach C_{max}
TQT	thorough QT
TTP	Time to Tumor Progression
TTR	Time to Tumor Response
ULN	upper limit of normal
UGT	uridine 5'-diphospho-glucuronosyltransferase
US	United States
VAS	Visual Analogue Scale
Vz/F	apparent volume of distribution
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 outwork 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 to 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 the 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 (**MRI slices of 1 mm for CNS lesions with a minimum size of 5 mm – 10 mm in size, MRI slices of 5 mm for CNS lesions greater than 10 mm**); up to 5 CNS lesions will be permitted in addition to 5 extracranial lesions previously**

noted.[31] Target lesions should be selected on the basis of the size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). Target intracranial lesions need to be suitable for accurate measurements with a minimum size of 5 mm by brain MRI or CT or no less than double the slice thickness, whichever is largest.

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 evaluated	No	PR
SD	Non-PD or Not 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 permanent discontinuation of treatment per the investigator's judgement 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

Hematology	**Chemistry Panel**	**Urinalysis**[§]	**Coagulation Tests**
Hemoglobin	ALT[1]	Protein, glucose and blood 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[1]		aPTT
WBC	Alkaline Phosphatase		
Absolute Neutrophils[2]	Sodium		
Absolute Lymphocytes[2]	Potassium		
Absolute Monocytes[2]	Magnesium		
Absolute Eosinophils[2]	Chloride		
Absolute Basophils[2]	Calcium		
	Total Bilirubin[1]		
	BUN or Urea[1]		
	Creatinine[1]		
	Glucose[1]		
	Phosphorus or Phosphate		
	Albumin[1]		
Lipids[1]	Total Protein[1]	Pregnancy Tests	
Total Cholesterol[1]	Uric Acid[1]	For female patients of childbearing potential, serum or urine	
LDL[1]	Amylase^[1]		
HDL[1]	Gamma glutamyl transferase (GGT)		
Triglycerides[1]	Lactate dehydrogenase (LDH)		
	Lipase[1]		
Infections			
HBV, HCV (Screening only and if clinically indicated in case infection status is unknown)			

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, total bile acids, alkaline phosphatase, and acetaminophen levels and/or protein adduct 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.

1. The laboratory results in fasted condition are suggested as applicable per CTCAE version 4.03 guidelines.
2. If absolute values are not reported as per local laboratory standard practice, percentages (%) are acceptable.

ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, GGT=gamma-glutamyltransferase, HDL=High density lipoprotein, INR=international normalized ratio, LDH=lactate dehydrogenase, LDL=Low density protein, 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)[33]

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.