A PHASE 1 STUDY TO EVALUATE THE EFFECT OF HEPATIC IMPAIRMENT ON THE PHARMACOKINETICS AND SAFETY OF LORLATINIB IN ADVANCED CANCER PATIENTS

Investigational Product Number:	PF-06463922
Investigational Product Name:	Lorlatinib
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Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	25 June 2018	Not applicable (N/A)
Amendment 1	11 Jan 2019	1. SOA: Hematology, Blood Chemistry, Coagulation, and Lipids as well as LVEF assessments, clarified that assessments are not required for Cycle 1 Day 1 if screening tests were done within 7 days prior to Cycle 1 Day 1. 2. SOA, physical examination, removed last sentences to reduce confusion. 3. SOA, urinalysis, added assessments in day 1 of each cycle. 4. SOA, 12-Lead ECG, the assessment of single reading ECG frequency changed from every other cycle to every cycle after cycle 3 day 1. 5. SOA, Tumor Assessments, added additional clarification. 6. SOA, End of Treatment/Withdrawal, changed from "… during the previous 4 weeks…" to "… during the previous 3 weeks…", as the treatment cycle is 3 weeks for this study. 7. Section 2, added AUC_{24}, C_{max}, C_{last}, T_{last} after single dose, T_{max} at steady state for lorlatinib, C_{last} after single dose and at steady state for metabolite as secondary endpoints. 8. Section 4.2, exclusion criteria updated according to new program level guideline. 9. Section 4.3.1, updated according to new program level guideline. 10. Section 4.3.2, corrected the drug name from crizotinib to lorlatinib. 11. Section 5.5, updated dose modification table

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		according to lorlatinib Core Data Sheet. 12. Section 5.9.1, updated to be consistent with product label and other studies. 13. Section 5.9.6 Anti Diarrheal, Anti-Emetic Therapy, deleted as it is not relevant for this study. 14. Section 5.9.7, Anti-Inflammatory Therapy, deleted as it is not relevant for this study. 15. Section 5.9.8, Corticosteroids, deleted as it is not relevant for this study. 16. Section 7.1, sentence "Ophthalmologic examinations will be performed in all patients" was deleted as it is not applicable for this study. 17. Section 7.1.1, updated to be consistent with other lorlatinib protocol. 18. Section 7.1.3, Table 7, updated to include direct bilirubin and make some corrections and clarifications for urinalysis and glucose, etc. 19. Section 7.1.5, deleted sentence "Two blood pressure readings will be taken at least 1 hour apart at each clinic visit", as it was not applicable for this study. 20. Section 7.1.6, minor editing. 21. Section 7.2.1, blood volume was reduced from 8.0 mL to 5.0 mL as only two 1 mL samples are required with more information available for metabolic profile of lorlatinib. 22. Section 7.3, minor editing. 23. Section 7.6, added reference for C-SSRS and minor editing. 24. Section 9.3.2, Table 9, definition for T_{last} was

Document	Version Date	Summary of Changes and Rationale
		added.
Amendment 2	14 November 2019	This amendment is intended to adjust the Inclusion criteria to allow more robust patient enrollment while ensuring patients' safety: 1. SOA: ECOG performance was added on Cycle 2 Day 1. 2. SOA: clarified the days for LFT assessment to make the table, footnote and section 7.1.4 clear and consistent. 3. Section 3.1, page 29, the second line under Table 4, "Table 6" should be referenced. 4. Section 4.1, Inclusion criterion #1, added "who have the capability to consent for themselves" to the end. 5. Section 4.1, the following Inclusion criteria are updated: a. #6: Platelets changed from "≥100,000/mm^3" to "≥50,000/mm^3"; Hemoglobin from "9 g/dL" to "≥8 g/dL". b. #7: both serum total amylase and lipase changed from "≤1.5 x ULN" to "≤2.0 x ULN without symptom of acute or chronic pancratitis". c. #8: Adequate Renal Function changed from "Serum creatinine ≤1.0 x ULN or CL_{cr} ≥90 mL/min as calculated using the method standard for the institute" to "eGFR ≥60 mL/min/1.73m^2 calculated using the Modification of Diet in Renal Disease (MDRD) equation". 6. Section 4.1, Inclusion criterion #11, deleted "or a legally acceptable representative)". 7. Section 4.2, Exclusion criterion #13, PR changed from ">220 msec" to ">200 msec";

Document	Version Date	Summary of Changes and Rationale
		deleted “unless patient is otherwise healthy such as long distance runner, etc.)”. 8. Section 4.2, Exclusion criterion #24, deleted “in the past 6 months”. 9. Section 5.4, page 41, the second line under Table 5, “Table 6” should be referenced. 10. Appendix 1: Addition of eGFR and HRT in the table.

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LIST OF TABLES

APPENDICES

SCHEDULE OF ACTIVITIES

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

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

	Screening[1]	Study Treatment[2]						End of Treatment /withdrawal[24]	Follow up[25]
		CYCLE 1 (21 Days)			CYCLE 2 (21 Days)		CYCLE ≥3 (21 Days)		
Visit Identifier[a]	**≤28 days prior to first dose**	**Day 1[3]**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		
Visit Window		**-1**	**±2**	**±2**	**±2**	**±2**	**±2; ±7 for LVEF and imaging**		
Informed consent[4]	X								
Medical/oncology history[5]	X	X							
Baseline signs and symptoms[6]		X							
Physical examination[7]	X	X	X	X	X		X	X	X
ECOG Performance status[8]	X	X			X		X	X	
Liver Function Assessment[9]	X	X	X	X	X	X	X	X	
Laboratory									
Hematology[10]	X	(X)	X	X	X		X	X	
Blood Chemistry[10]	X	(X)	X	X	X		X	X	
Coagulation[10]	X	(X)	X	X	X		X	X	
Lipids[10]	X	(X)	X	X	X		X	X	
Urinalysis[11]	X	(X)			X		X	X	
HBV, HCV	X								
Pregnancy test[12]	X	X			X		X	X	
Contraception check[13]	X	X	X	X	X		X	X	X
12 Lead ECG[14]	X	X	X	X	X		X	X	
LVEF assessment[15]	X	(X)					X (every odd-numbered cycle)	X	
Enrollment and Treatment									
Enrollment[16]		X							
Lorlatinib administration		Orally on a continued QD dosing regimen							

	Screening[1]	Study Treatment[2]						End of Treatment /withdrawal[24]	Follow up[25]
		CYCLE 1 (21 Days)			CYCLE 2 (21 Days)		CYCLE ≥3 (21 Days)		
Visit Identifier[a]	**≤28 days prior to first dose**	**Day 1[3]**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**		
Visit Window		**-1**	**±2**	**±2**	**±2**	**±2**	**±2; ±7 for LVEF and imaging**		
Tumor assessments[17]									
CT or MRI scan or equivalent	X						X (Every odd-numbered cycle or according to the standard practice at the site)	X	
Other clinical assessments									
Serious and non-serious adverse event monitoring[18]	X	→	→	→	→		→	→	X
Concomitant treatment(s)[19]	X	→	→	→	→		→	→	X
Suicidal Ideation and Behavior[20]		X			X		X (up to Cycle 6 and then Day 1 of every other cycle)	X	
Other assessments									
Pharmacokinetics[21]		X	X	X	X				
CCI [redacted]		[redacted]							
[redacted]		[redacted]							

Abbreviations: → = ongoing/continuous event; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ECHO = echocardiogram; HBV = hepatitis B virus; HCV = hepatitis C virus; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; RECIST= Response Evaluation Criteria for Solid Tumors. (X) – to be completed if not performed within 7 days of the first dose of lorlatinib.

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

1. **Screening:** To be obtained within 28 days prior to the start of study treatment.
2. **Study Treatment:** All assessments should be performed prior to dosing with lorlatinib unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. All cycles are 21 days in duration. Following completion of Cycle 2, ongoing patients on lorlatinib will need to visit the clinic on Day 1 of every cycle for assessments. Enough study medication for one cycle of treatment will be dispensed at each clinic visit. Some assessments such as Liver Function Assessment and physical examination could be performed more frequently at the discretion of investigator according to the standard practice at the site. Tumor assessments may occur at every odd-numbered cycle or according to standard practice for the indication at the site.
3. **Cycle 1/Day 1:** Blood chemistry, hematology, coagulation, lipids, and physical examination not required if acceptable corresponding screening assessment was performed within 7 days prior to the start of study treatment. Values closest prior to the first dose of lorlatinib will be used for baseline.
4. **Informed Consent:** Must be obtained prior to undergoing any study-specific procedures.

5. **Medical/Oncological History:** To also include information on prior medications, smoking history, prior treatment regimens. Will be updated on Cycle 1 Day 1 before the start of treatment.
6. **Baseline Signs & Symptoms:** Patients will be asked about any signs and symptoms experienced within the 14 days prior to the first dose of lorlatinib on Cycle 1 Day 1 (as baseline values).
7. **Physical Examination:** Includes an examination of major body systems, height (at screening only), weight, blood pressure and pulse rate, and will be conducted weekly in the first cycle, on the first day of the following cycles, at the end of treatment, and at the follow-up visit.
8. **Performance Status:** Use ECOG classification – see Appendix 2.
9. **Liver Function Assessment:** Liver function will be assessed during screening and confirmed before the start of lorlatinib treatment. Liver Function Assessment should at least include tests for AST, ALT, albumin, alkaline phophatase, total bilirubin, and direct bilirubin. Tests done for blood chemistry can be used for liver function assessment. Additional tests should be performed to complete the liver function assessment if necessary. All liver function assessments for patient categorization must be completed within 24 hours prior to the start of lorlatinib treatment on Cycle 1 Day 1. Patients will be assigned to different groups according to their liver function before the start of lorlatinib treatment. Criteria for stratification based on liver function are provided in Section 3.1 of the protocol. Liver function assessments will be performed weekly until the start of Cycle 2, on Cycle 2 Day 15, on day 1 of each following cycle, at the End of Treatment, and as clinically indicated. There should be more frequent testing for liver function in case of Grade 2-4 elevations or in case of signs or symptoms consistent with hepatotoxicity or hepatic failure (eg, fatigue, weakness, anorexia, nausea, vomiting, right upper quadrant adnominal pain, jaundice, dark urine, and in rare cases, fever and rash). More frequent monitoring could be performed as the discretion of investigator at any time. Child-Pugh scores will also be calculated and recorded in conjunction with liver function tests prior to the start of the first lorlatinib dose, but will not be used to stratify patients. Liver function tests should be repeated within 48 hours if the following is observed and repeated weekly until recovery to baseline levels: If **a patient entered study with AST or ALT** baseline values within the normal range who subsequently presented with AST or ALT ≥3 × ULN concurrent with total bilirubin ≥2 × ULN, OR **a patient with baseline AST or ALT values** above the normal range who subsequently presented with AST or ALT ≥2 × the baseline values concurrent with a total bilirubin increased by ≥2 × baseline or >3 × ULN (whichever is smaller) and alkaline phosphate <2 × ULN or not available. A 4-mL serum sample obtained just prior to the first dose of lorlatinib will be stored frozen on site through completion of the study for possible use as a baseline reference should additional laboratory tests be indicated, for example, additional testing to exclude other causes of liver injury (see ADVERSE EVENT REPORTING).
10. **Hematology, Blood Chemistry, Coagulation, and Lipids**: will be performed at screening, days 1, 8 and 15 in Cycle 1, and Day 1 of every cycle thereafter. More frequent monitoring could be performed at the discretion of the investigator or when clinically indicated. Cycle 1 Day 1 tests will only be required if the screening tests were not done within 7 days. Required tests are listed in Section 7.1.3 of the protocol.
11. **Urinalysis**: Dipstick is acceptable. Microscopic analysis to be conducted if dipstick abnormal and/or if this is the local standard. Will be performed at screening and Day 1 of each cycle and repeated as clinically indicated, for example, upon diagnosis of renal cysts (more frequent assessment may be performed based on local requirement). See ASSESSMENTS section for Laboratory Tests list. Cycle 1 Day 1 tests will only be required if the screening tests were not done within 7 days.
12. **Serum or Urine Pregnancy Test:** For female patients of childbearing potential, a serum or urine pregnancy test, must be performed on two occasions prior to starting study therapy, once at screening (serum) and once at the baseline visit (serum or urine, prior to the first lorlatinib dose), whose results must be available before lorlatinib administration. Pregnancy tests also need to be routinely repeated at every cycle during the active treatment period, at the end of treatment and additionally whenever one menstrual cycle is missed or when potential pregnancy is otherwise suspected. Additional pregnancy tests to be conducted if requested by IRB/IECs or by local regulations.
13. **Contraception Check:** Male patients who are able to father children and female patients who are of childbearing potential will need to follow the contraception guidelines in Section 4.3.1.

14. **12-Lead ECG**: Triplicate ECG will be performed at screening, times 0 (predose) 1, 2, 4, 10 and 24 hours post dose on Cycle 1 Day 1 and Cycle 2 Day 1, predose on days 8 and 15 in cycle 1, and at the end of treatment. At each time point, 3 consecutive 12-lead ECGs are to be performed approximately 2 minutes apart. The ECG must occur prior to any blood sample collections or venipuncturing or collection of vital signs. All ECGs scheduled at 0 hours must be collected prior to dosing. All efforts should be made to ensure the ECG collections completed within 15 minutes prior to the PK collection if they are planned at the same time. Additional ECGs may be collected as clinically indicated. Single reading ECG will be collected pre-dose on Day 1 of Cycle 3 and every cycle thereafter.
15. **LVEF Assessment:** Echocardiogram or MUGA to be performed at Screening, at pre-dose (0 hour) on Cycle 1 Day 1 (not required if screening LVEF was obtained within 7 days prior to Cycle 1 Day 1) and on Day 1 of every other cycle thereafter, and at the EOT visit. The same method should be used at each time point.
16. **Enrollment**: Enrollment number and treatment group allocation assigned by Pfizer Inc based on AST and total bilirubin values.
17. **Tumor Assessments**: Tumor assessments will include all known or suspected disease sites. Imaging may include CT or MRI scans of chest, abdomen, and pelvis. Brain scans and bone scans will be performed at screening if disease is suspected and on study as appropriate to follow disease. The Investigator evaluation will be used for response analysis according to RECIST v1.1. Tumor assessment should be repeated at the end of treatment visit if more than 6 weeks have passed since the last evaluation.
18. **Serious and non-serious adverse event monitoring**: 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 SAEs ("active collection period") for each patient begins from the time the patient provides informed consent through and including a minimum of 28 calendar days after the last lorlatinib administration. If the patient begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment.
19. **Concomitant Treatments**: All concomitant medications and NonDrug Supportive Interventions should be recorded on the CRF from 28 days prior to start of the study treatment and up to 28 days after the last dose of study treatment.
20. **Suicidal Ideation and Behavior:** An assessment of suicidal ideation and behavior via the Columbia Suicide Severity Rating Scale (C- SSRS) will be administered to patients prior to the first day of investigational drugs dosing (ie, Cycle 1 Day1) and then prior to dosing on Day 1 of Cycle 2 through Cycle 6. After Cycle 6 Day 1, this test will be administered prior to dosing on Day 1 of every other cycle (ie, Cycle 8 Day 1, Cycle 10 Day 1, etc.) and at EOT.
21. **Pharmacokinetics** plasma samples for characterization of pharmacokinetics (PK) of lorlatinib and its metabolite(s) will be collected at times 0 (predose), 0.5, 1, 2, 4, 6, 10, and 24 hours post lorlatinib dose on Cycle 1 Day 1 and Cycle 2 Day 1. Predose PK samples will also be collected prior to the lorlatinib dose on Days 8 and 15 of Cycle 1.

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24. **End of Treatment/Withdrawal:** Obtain these assessments if not completed during the previous 3 weeks on study (last 6 weeks for tumor assessments). If the subject withdraws from lorlatinib treatment during a cycle visit, then this will be considered the subject's End of Treatment visit.
25. **Follow up:** At least 28 calendar days, and preferrable no more than 35 calendar days, after discontinuation of treatment, patients will return to undergo review of concomitant treatments, vital signs, contraception check, and assessment for resolution of any treatment-related toxicity. Patients continuing to experience toxicity at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.

Pharmacokinetic and ECG Sampling Schema

Hours post lorlatinib dose	0 (predose)	0.5	1	2	4	6	10	24
Cycle 1 Day 1								
Plasma sample for PK analysis	X	X	X	X	X	X	X	X
12 Lead ECG	X		X	X	X		X	X
Cycle 1 Days 8 and 15								
Plasma sample for PK analysis	X							
Cycle 2 Day 1								
Plasma sample for PK analysis	X	X	X	X	X	X	X	X
12 Lead ECG	X		X	X	X		X	X

Abbreviation: PK = pharmacokinetics: ECG=electrocardiogram

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Lorlatinib is a selective, adenosine triphosphate (ATP) competitive small molecule tyrosine kinase inhibitor (TKI) of the Anaplastic Lymphoma Kinase (ALK)-positive or c-ROS oncogene 1 (ROS1)-positive receptor tyrosine kinases (RTK) that also potently inhibits ALK kinase domain mutations responsible for resistance to crizotinib. Lorlatinib is currently being developed as a novel anticancer agent for the treatment of patients with ALK-positive or ROS1-positive advanced non small-cell lung cancer (NSCLC).

1.2. Background and Rationale

1.2.1. Background

In 2007, two research groups independently reported the discovery of an NSCLC oncogenic fusion gene (echinoderm microtubule associated protein like 4 [EML4] ALK) that combines portions of the EML4 gene and the ALK gene.[1,2] This fusion gene encodes for the cytoplasmic fusion protein EML4 ALK which upon dimerisation, results in constitutive activation of the kinase domain of ALK. ROS1 fusions were identified as potential driver mutations in a NSCLC cell line (HCC78: SLCA2 ROS1) and a NSCLC patient sample (CD74 ROS1).[1] Approximately 3- 5% of NSCLC is molecularly defined as ALK-positive and 1- 2% as ROS1-positive.[3,4]

In vivo, lorlatinib demonstrated marked cytoreductive activity in mice bearing tumor xenografts that express ALK or ROS1 fusion variants, including the crizotinib resistant EML4 ALK^{L1196M} or EML4 ALK^{G1269A} mutations.[5] Lorlatinib treatment also significantly reduced the tumor size and prolonged animal survival in the orthotopic brain models (EML4 ALK and EML4 ALK^{L1196M}) in mice.

The anti-tumor efficacy of lorlatinib was dose dependent and demonstrated strong correlations to inhibition of ALK or ROS1 phosphorylation. The plasma concentrations associated with inhibitory activity of lorlatinib against EML4 ALK^{L1196M} phosphorylation, and anti tumor efficacy in EML4 ALK^{L1196M} dependent human NSCLC cell line models, was utilized to project target human efficacious plasma concentrations for clinical studies. The predicted effective plasma concentration (C_{eff}) (unbound) for lorlatinib for EML4 ALK, EML4 ALK^{L1196M}, and EML4 ALK^{G1202R} is 6.5 nM, 51 nM, and 125 nM, respectively; when corrected for human plasma protein binding results in predicted efficacious concentration (C_{eff}) (total) of 7.6 ng/mL, 62 ng/mL, and 150 ng/mL, respectively.

1.2.1.1. Non Clinical Pharmacokinetics, Metabolism and Safety of Lorlatinib

Details of the nonclinical absorption, distribution, metabolism and excretion properties of lorlatinib are provided in the Investigator's Brochure (IB). Lorlatinib was well absorbed after a single oral dose to rats and dogs, with high oral bioavailability observed in both species (~100% rats; 97% dogs). Renal excretion of the parent drug was limited in rats and dogs. The fraction unbound of lorlatinib to plasma proteins were 0.303, 0.287, and 0.340 for rat, dog, and human, respectively.

In rats, dogs, and humans, lorlatinib undergoes metabolism via oxidation and/or glucuronidation. In vitro, lorlatinib was metabolized primarily by cytochrome P50 (CYP)3A4 and uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A4, with minor contributions from CYP2C8, CYP2C19, CYP3A5, and UGT1A3. In vitro, lorlatinib is not a substrate for the P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) efflux transporters nor for the hepatic uptake transporters organic-anion-transporting polypeptide (OATP)1B1 and OATP1B3.

The likelihood of metabolic drug-drug interaction (DDI) resulting from inhibition by lorlatinib of the clearance of concomitant drugs that are substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 is low at clinically relevant concentrations. In vitro, lorlatinib is a reversible and a time-dependent inhibitor of CYP3A4/5, and also induces CYP3A4 and activates human pregnane X receptor (hPXR). In humans, lorlatinib exhibited a net induction effect on CYP3A4/5. In vitro, lorlatinib induced CYP2B6 and activated hCAR1, and may have the potential for induction of drugs that are metabolized by CYP2B6. Induction of CYP1A2 by lorlatinib is unlikely at clinically relevant concentrations. PF-06895751, a major circulating metabolite for lorlatinib, is unlikely to cause DDI by induction of CYP1A2, CYP2B6, and CYP3A4, or inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

Assessments based on in vitro evaluations indicate that lorlatinib and PF-06895751 has a low risk to cause inhibitory pharmacokinetic DDI with substrates for UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15 at clinically relevant concentrations. The potential for lorlatinib to cause DDI by inhibiting BCRP (systemically), OATP1B1, OATP1B3, organic anion transporter (OAT)1, organic cation transporter (OCT)2, and multidrug and toxin extrusion 2K (MATE2K) was low at clinically relevant concentrations, but may have the potential to inhibit P-gp (systemically and gastrointestinal [GI] tract), BCRP (GI tract), OCT1, OAT3, and MATE1. PF-06895751 is unlikely to cause DDI by inhibiting these evaluated drug transporters at clinically relevant concentrations.

Lorlatinib was administered to rats and dogs in toxicity studies up to 13 weeks in duration with twice daily (BID) dosing. Moribundity preceded by clinical signs of intolerance was observed in repeat-dose toxicity studies at 60 mg/kg/day in rats and 50 mg/kg/day in dogs where systemic exposure exceeded exposure at clinically relevant doses. Based on the nonclinical safety studies conducted with lorlatinib, the important toxicities included changes associated with inflammation across multiple tissues, and changes in the pancreas (degeneration and/or atrophy of pancreatic acinar cells and associated higher amylase and lipase), hepatobiliary system (bile duct hyperplasia and elevations in alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], glutamate dehydrogenase [GLDH], and/or gamma-glutamyl transferase [GGT]), male reproductive system (degeneration of seminiferous tubules in the testis and epididymal inflammation), cardiovascular system (see below), and gastrointestinal tract (emesis, ulceration/erosion, edema) of rats and/or dogs. Additional important findings were observed in peripheral nerves (axonal degeneration), central nervous system (CNS) (cognitive and neurological function), and the kidney (glomerulopathy, hyaline casts, arterial degeneration/necrosis, tubular basophilia/pigmentation) of rats. Reversibility (full or partial) was established for all lorlatinib-related target organ toxicities with the exception of hepatic

bile duct hyperplasia after 13 weeks of lorlatinib administration in rats. Lorlatinib was evaluated in in vitro, ex vivo, and/or in vivo safety pharmacology studies to identify potential effects on the cardiovascular system. Lorlatinib was identified as a weak inhibitor of the human Ether-a-go-go-Related Gene (hERG) potassium channel and L-type calcium channels, and also increased late sodium currents. Lorlatinib increased PR and QRS intervals ex vivo and/or in vivo and induced changes in blood pressure and heart rate in vivo. Non-adverse histological changes in the heart and increases in heart weight were also observed after administration of lorlatinib for ≥4 weeks to rats. The potential for mild, non-dose dependent impairment of cognitive function in rats was identified in a contextual renewal model. Lorlatinib was also associated with the potential for embryo-fetal toxicity and was identified as an aneugen. Some of the nonclinical findings were likely due to off-target inhibition of tropomyosin receptor kinase B (TrkB) including effects on the peripheral and central nervous system, and changes in lipid profiles and body weight. The major human circulating metabolite PF-06895751 did not show primary or secondary pharmacologic activity against ALK and ROS1 kinase targets, or against a broad panel of receptors, enzymes, transporters, and ion channels. PF-06895751 did not inhibit the hERG potassium channel and was not genotoxic. The no-observed-adverse-effect-level (NOAEL)s in the pivotal 13-week toxicity studies were 8/4 mg/kg/day in male/female rats (unbound maximal plasma concentration [C_{max}] of 442/451 ng/mL and area under the curve [AUC] of 6240/7820 ng•hr/mL and associated AUC exposure margins of 3.3/4.1x at the recommended human dose of 100 mg once a day [QD]) and 7 mg/kg/day in dogs (unbound C_{max} of 330 ng/mL and AUC of 2980 ng•hr/mL and an associated AUC exposure margin of 1.6x). Further details of the nonclinical safety program are provided in the current Investigator's Brochure.

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

1.2.1.2. Clinical Summary

1.2.1.2.1. Safety and Pharmacokinetics

There are three ongoing clinical studies with lorlatinib in patients with ALK-positive or ROS1-positive NSCLC. B7461001 is a single-agent study currently in Phase 2 and described in detail below. B9991005 is a Phase 1b/2 study to evaluate the combination of lorlatinib with avelumab. B7461006 is an open-label, multicenter, randomized Phase 3 study comparing lorlatinib to crizotinib in treatment-naïve ALK-positive advanced NSCLC.

Seven (7) healthy volunteer studies that have been completed are described in detail below and include B7461004, B7461005, B7461007, B7461008, B7461011, B7461012, B7461016 and B7461017. These studies also utilized the recommended Phase 2 dose (RP2D) of 100 mg QD as a single dose administration. B7461004 and B7461017 are completed radiolabelled mass balance studies. B7461005 is a completed relative bioavailability study. B7461007 is a completed study which estimated the absolute oral bioavailability of lorlatinib. B7461008 is a completed study which evaluated the effects of acid-reducing agents and food on pharmacokinetics (PK) of lorlatinib. Study B7461011 evaluated the effect of a strong enzyme inducer rifampin on the PK of single-dose lorlatinib. B7461012 is a completed study that evaluated the effect of a strong CYP3A4/5 inhibitor, itraconazole, on the PK of single-dose lorlatinib. B7461016 is a completed bioequivalence study.

1.2.1.2.1.1. Study B7461001

Study B7461001 is a Phase 1/2, open-label, multicenter, multiple-dose, dose-escalation, safety, PK, pharmacodynamic (PD) and anticancer efficacy exploration study of lorlatinib as a single-agent in patients with ALK-positive or ROS1-positive advanced NSCLC.

B7461001 is being conducted in 2 parts: Phase 1 and Phase 2. The Phase 1 portion of the study was aimed at estimating the maximum tolerated dose (MTD) for single-agent lorlatinib in dose-escalation cohorts in patients with ALK-positive or ROS1-positive advanced NSCLC with or without asymptomatic central nervous system (CNS) metastases, and was planned to enroll up to 36 patients (depending on toxicities observed). The Phase 2 portion of the study is being conducted with single-agent lorlatinib at the identified recommended Phase 2 dose (RP2D) and is enrolling patients with ALK-positive NSCLC or ROS1-positive advanced NSCLC, with or without asymptomatic CNS metastases.

The Phase 1 portion of this study employed a modified continual reassessment method (CRM) to estimate the MTD. The CRM was initiated at 25 mg QD and recommended escalation to 75, 100, 150, and 200 mg QD based on no dose limiting toxicities (DLTs) observed at the previous dose levels tested. At 200 mg QD, one (1) DLT occurred in a patient who failed to receive 16 of the planned 21 lorlatinib doses in Cycle 1 due to Grade 1 vision change, abnormal dreams and photosensitivity reaction, and Grade 2 aphasia and cognitive disorder. Although the CRM model recommended continuation to the next higher dose above 200 mg QD, a decision was made among the treating investigators and the sponsor to re-test lower doses (ie, outside of the CRM model) to better understand and evaluate the CNS effects observed at the higher dose levels. These CNS effects observed consisted of mostly Grade 1 and Grade 2 transient effects including changes in speech, cognition, memory and mood.

Overall, 100 mg QD was a well-tolerated dose. None of the patients at this dose required dose reduction and dose delays were not attributed to CNS effects, but rather to hypercholesterolemia or hypertriglyceridemia or disease related events. The data from the dose escalation portion of B7461001 study identified lorlatinib to be well tolerated. Based on the PK data observed, simulated patient exposure showed the 100 mg QD dose to be the lowest dose exceeding the lorlatinib C_{eff} of 150 ng/mL during the majority of the dosing cycle once steady-state was reached. The C_{eff} of 150 ng/mL was a concentration predicted to result in >80% tumor growth inhibition of the ALK^{G1202R} resistance mutation.

The 100 mg QD dose was chosen as the RP2D based on the entirety of the safety, efficacy, and clinical pharmacology data. The RP2D was not based on formal DLT and MTD determinations due to the nature of the cognitive effects.

As of March 2017, lorlatinib had been administered to a total of 54 patients across 7 QD doses (10, 25, 50, 75, 100, 150, and 200 mg) and 3 twice a day (BID) doses (35, 75, and 100 mg). The most commonly occurring treatment-related adverse event (AE) was HYPERCHOLESTEROLEMIA reported in 72.2% patients, EDEMA reported in 53.7% of patients and HYPERTRIGLYCERIDEMIA reported in 42.6% of patients, PERIPHERAL NEUROPATHY reported in 40.7% of patients, and COGNITIVE EFFECTS reported in 25.9% of the patients. All of the treatment-related AEs were reported with a maximum

common terminology criteria (CTC) Grade 3, with the exception of 3 patients with Grade 4 HYPERCHOLESTEROLEMIA and 1 patient with Grade 4 gamma-glutamyltransferase increased. Of note, terms that are in all capitalized letters are cluster terms as defined in the Investigator's Brochure (IB).

The Phase 2 began enrollment in September 2015. Enrollment has been rapid, with 111 patients dosed as of March 2017. The overall the safety profile has been consistent with that observed in the Phase 1.

As of March 2017, single and multiple dose PK data from Phase 1 have been analyzed from 10-200 mg QD and 35-100 mg BID dose cohorts. All 54 patients had at least 1 measurable PK concentration and 1 PK parameter of lorlatinib. PK parameters are summarized in Table 1 and Table 2 after single and multiple dose administration.

Table 1. Summary of Lorlatinib Single Dose PK Parameters – B7461001 Phase 1

Day -7 Lead In: *QD Doses*	*10 mg QD*	*50 mg QD*	*75 mg QD*	*100 mg QD*	*200 mg QD*
N, n	3,1	2,2	12,11	16,15	3,3
AUC_{inf} [ng•hr/mL]	698.0	(7210,7240)	7663 (79)	8236 (25)	18340 (61)
AUC_{inf}(dn)[ng•hr/mL/mg]	69.80	(144,145)	102.2 (79)	82.36 (25)	91.68 (61)
AUC_{tau} [ng•hr/mL]	488.2 (21)	(3310, 3880)	3990 (55)	5110 (28)	11410 (43)
AUC_{tau}(dn)[ng•hr/mL/mg]	48.82 (21)	(66.1, 77.7)	53.14 (54)	51.10 (28)	57.13 (43)
CL/F [L/hr]	14.30	(6.91, 6.94)	9.788 (79)	12.14 (25)	10.90 (61)
C_{max} [ng/mL]	50.80 (17)	(390, 423)	489.1 (45)	595.5 (37)	1201 (19)
C_{max}(dn) [ng/mL/mg]	5.080 (17)	(7.80, 8.46)	6.523 (45)	5.955 (37)	6.003 (19)
MRT [hr]	23.7	(27.7, 43.1)	36.0 ± 11.7	27.0 ± 7.04	25.8 ± 6.36
T_{max}[hr]	1.98 (1.00-2.97)	1.25 (0.500-2.00)	1.09 (0.500-4.03)	1.96 (0.517- 4.33)	2.00 (1.18- 3.00)
Vz/F [L]	373.0	(166, 307)	367.9 (54)	356.3 (39)	307.8 (41)
$t_{½}$ [hr]	18.0	(16.6, 30.8)	27.2 ± 8.30	20.9 ± 5.03	19.8 ± 3.30
Day -7 Lead In: *BID Doses*	*35 mg BID*	*75 mg BID*	*100 mg BID*		
N, n	3,2	3,1	4,4		
AUC_{inf} [ng.hr/mL]	(2630, 3690)	6860	6318 (56)		
AUC_{inf}(dn)[ng.hr/mL/mg]	(75.1, 105)	91.40	63.18 (56)		
AUC_{tau} [ng.hr/mL]	982.4 (9)	2996 (20)	2925 (47)		
AUC_{tau}(dn)[ng.hr/mL/mg]	28.03 (9)	40.00 (20)	29.25 (47)		
CL/F [L/hr]	(9.48, 13.3)	10.9	15.83 (56)		
C_{max} [ng/mL]	202.2 (57)	594.9 (27)	507.2 (51)		
C_{max}(dn) [ng/mL/mg]	5.776 (57)	7.933 (27)	5.072 (51)		
MRT [hr]	(30.8, 37.7)	33.0	22.1 ± 6.76		
T_{max}[hr]	1.20 (0.500- 1.97)	1.23 (1.00- 2.00)	2.00 (1.10-3.07)		
V_z/F [L]	(362, 472)	410.0	378.3 (54)		
$t_{½}$ [hr]	(24.6, 26.5)	26.00	17.18 ± 5.19		
Cycle 1 Day 1: QD Doses	25 mg QD	150 mg QD			
N, n	3,3	3,3			
AUC_{tau}[ng.hr/mL]	1387 (35)	7474 (73)			
AUC_{tau}(dn) [ng.hr/mL/mg]	55.49 (35)	49.80 (73)			
C_{max} [ng/mL]	149.2 (71)	760.0 (58)			
T_{max} [hr]	2.00 (0.500- 2.05)	1.05 (1.00-3.00)			

Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean ± Std Dev for $t_{½}$ and MRT. The single observation was reported when n=1 and the range was reported when n=2.
N = Number of patients in the treatment group; n= number of patients where $t_{½}$, MRT, $AUC_{inf,}$ CL/F and V_z/F were determined.
Source: Table 14.4.4.1.1.1

Table 2. Summary of Lorlatinib Steady State PK Parameters After Repeated QD Dosing – B7461001 Phase 1

Cycle 1 Day 15: *QD Doses*	*10 mg QD*	*25 mg QD*	*50 mg QD*	*75 mg QD*	*100 mg QD*	*150 mg QD*	*200 mg QD*
N,n[b], n[c]	3, 3, 1	3, 3, 0	3, 2, 2	12, 12, 11	16, 15, 14	3, 3, 0	2, 2, 2
AUC_{tau} [ng•hr/mL]	752.1 (26)	1701 (29)	3367 (39)	4107 (53)	5121 (30)	6157 (9)	(4480, 12900)
AUC_{tau}(dn) [ng•hr/mL/mg]	75.21 (26)	68.12 (29)	67.50 (39)	56.62 (48)	51.21 (30)	41.02 (9)	(22.4, 64.7)
CL/F [L/hr]	13.27 (26)	14.72 (29)	14.84 (39)	176.66 (48)	19.52 (30)	24.37 (9)	(15.5, 44.6)
C_{max} [ng/mL]	67.29 (18)	138.1 (35)	359.7 (27)	429.6 (48)	550.2 (32)	541.0 (42)	(760, 1430)
C_{max}(dn) [ng/mL/mg]	6.729 (18)	5.522 (35)	7.193 (27)	5.925 (44)	5.502 (32)	3.604 (42)	(3.80, 7.15)
R_{ac}	1.54 ± 0.075	1.24 ± 0.210	(0.879, 1.33)	1.12 ± 0.446	1.07 ± 0.311	1.00 ± 0.791	(0.571, 0.729)
R_{ss}	0.993	ND	(0.401, 0.719)	0.613 ± 0.290	0.660 ± 0.186	ND	(0.384, 0.403)
T_{max} [hr]	1.00 (1.00-1.08)	1.00 (1.00-2.00)	2.00 (1.92-2.75)	1.03 (0.500-2.00)	1.13 (1.00-4.00)	1.30 (1.00-24.0)	1.61 (1.22-2.00)
Cycle 1 Day 15: *BID Doses*	*35 mg BID*	*75 mg BID*	*100 mg BID*				
N,n[b], n[c]	1, 1, 1	3, 3, 1	3, 3, 3				
AUC_{tau} [ng•hr/mL]	2140	3574 (35)	4058 (33)				
AUC_{tau}(dn) [ng•hr/mL/mg]	61.30	47.67 (35)	44.66 (47)				
CL/F [L/hr]	16.30	20.99 (35)	22.37 (47)				
C_{max} [ng/mL]	370.0	550.0 (23)	600.5 (27)				
C_{max}(dn) [ng/mL/mg]	10.60	7.333 (23)	6.609 (37)				
R_{ac}	2.090	1.23 ± 0.352	1.52 ± 0.296				
R_{ss}	0.8150	0.5420	0.769 ± 0.136				
T_{max} [hr]	0.500	0.550 (0.500-2.05)	2.00 (1.00-2.00)				

Source: B7461001 CSR Table 14.4.4.1.1.1.
N = Number of patients in the treatment group; n[b]=number of patients where R_{ac} were determined; n[c]=number of patients where R_{ss} were determined.
Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean± Std Dev for $t_{½}$, MRT R_{ac} and R_{ss}. Single observation was reported when n=1 and range when n=2.
R_{ac} is the observed accumulation ratio calculated by Day 15 AUC_{tau}/Lead In Day -7 AUC_{tau} or Day 1 AUC_{tau}.
R_{ss} is the steady state accumulation ratio calculated by Day 15 AUC_{tau}/Lead In Day -7 AUC_{inf}.

After single oral administration of the acetate solvate form of lorlatinib under fasted conditions, median peak plasma concentrations were observed between 1 and 2 hours. Following attainment of C_{max}, lorlatinib plasma concentrations showed a bi-exponential decline with mean terminal elimination half-life ranging across the tested dose groups from 17.2 to 27.2 hours, mean apparent oral clearance (CL/F) of 9.8 to 15.8 L/hr and mean volume of distribution (V_z/F) of 308 to 410 L. Variability in PK was observed with a coefficient of variation (CV%) of 25-79% across tested doses for AUC_{inf} and 17-45% for C_{max} following single oral administration.

After repeated QD oral administration, steady state should have been achieved before Day 15 based on the lorlatinib apparent terminal elimination half-life (Table 3). The observed steady state accumulation rations (R_{ac} and R_{ss}, respectively) seemed to be less than the predicted values based on the calculated lorlatinib elimination rate and the frequency of administration, which suggests auto-induction may play a role in lorlatinib disposition. The auto-induction seems more prominant with increasing dose levels, as the observed accumulation index becomes smaller.

PK data (March 2017) after 100 mg single and multiple dosing in Phase 1 with acetate solvate drug form and in Phase 2 with free base drug form are summarized in Table 3.

Table 3. Summary of Lorlatinib 100 mg QD PK Parameters after Single and Multiple Doses in B7461001

Dose	N	AUC (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)	CL/F (L/hr)	V_z/F (L)
Phase 1: Acetate Solvate							
Single Dose	16	8236 (25)	595.5 (37)	1.96 (0.517-4.33)	20.9±5.03	12.14 (25)	356.3 (39)
Multiple Doses	16	5121 (30)	550.2 (32)	1.13 (1.0-4.0)	NA	19.52 (30)	NA
Phase 2: Free Base							
Single Dose	19	9088 (35)	695.2 (40)	1.55 (0.50-4.02)	23.6±9.37	11.01 (35)	351.5 (37)
Multiple Doses	26	5650 (39)	576.5 (42)	1.96 (0.50-22.7)	NA	17.70 (39)	NA

Source data: B7461001 CSR, Table 14.4.4.1.2.1.

Geometric mean (%CV) for AUC, C_{max}, CL/F, and V_z/F; arithmetic mean ± SD for $t_{1/2}$; median (range) for T_{max}.
AUC_{inf} for single-dose and AUC_{τ} for multiple doses.
V_z/F is calculated by Dose/(lambda Z x AUC_{inf}) for single dose.

In vitro data indicated that lorlatinib is associated with time-dependent inhibition and induction of CYP3A. In order to assess the net clinical effect of lorlatinib on CYP3A, the CYP3A substrate drug midazolam was given alone and 14 days after administration of 25 mg QD and 150 mg QD of lorlatinib to a total of 6 patients. Midazolam AUC_{last} geometric mean values (CV) decreased from 51.3 (47%) to 20.4 (18%) ng.hr/mL and from 36.5 (20%) to 14.4 (25%) ng.hr/mL, respectively, with 25 mg QD and 150 mg QD lorlatinib dosing. Likewise, midazolam C_{max} geometric mean values (CV) decreased from 16.1 (42%) to 9.7 (40%) ng/mL and from 11.6 (48%) to 5.73 (43%) ng/mL, respectively, with 25 mg QD and 150 mg QD lorlatinib dosing. These results indicated that at clinical dose levels, lorlatinib has the potential to reduce the exposure of CYP3A substrates. Concomitant use of lorlatinib with CYP3A substrates with narrow therapeutic indices should be avoided.

1.2.1.2.1.2. Study B7461004

Study B7461004 is a completed Phase 1 study which evaluated the mass-balance and PK of lorlatinib in 6 healthy male subjects after a single oral 100 mg dose of radiolabeled lorlatinib containing approximately 100 μCi of [^{14}C]lorlatinib.

The results indicate a mean of 47.73% of the radioactivity was recovered in urine and 40.91% was recovered in feces through the last collection interval. Most of the administered radioactivity was recovered in the first 144 hours postdose (85.11%). The overall mean recovery of radioactivity in urine and feces samples was 88.64% over the 288-hour study, with recovery in individual subjects ranging from 83.6 to 90.8%. The urinary excretion of unchanged lorlatinib was found to be a minor route of elimination with less than 1% of the administered parent drug, excreted unchanged in the urine over the 168-hour collection period. The geometric mean renal clearance (CL_R) was 1.57 mL/min.

Metabolic profiling indicates that the major circulating metabolite was a benzoic acid metabolite resulting from cleavage of the ring structure of lorlatinib and accounting for 21.0% of the total circulating radioactivity in plasma. The plasma concentration of this metabolite (PF-06895751) is currently monitored in clinical studies. In the urine, the 2 major metabolites identified were an N-oxide and a glucuronide product, accounting for 16.3% and 10.9% of the dose, respectively. In the current B7461009 study, samples will be collected to describe the PK of lorlatinib metabolite(s).

1.2.1.2.1.3. Study B7461017

Study B7461017 is a completed Phase 1 Study which evaluate the mass-balance and PK of lorlatinib in 6 healthy male subjects after a single oral 100 mg dose of radiolabeled lorlatinib containing approximately 100 μCi of [^{14}C]lorlatinib. The ^{14}C label is placed in the other half of the ring structure compared to the ^{14}C label in study B7461004. The results from the two studies fully characterized the metabolic pathway of lorlatinib.

The overall mean cumulative recovery of radioactivity from urine and fece are 91.59% over the 264 hour collection period with recovery in individual subjects ranging from 84.6 to 94.3%. A mean of 63.69% of the dose was recovered in feces and 27.90% was recovered in urine. Most of the administered radioactivity was recovered in the first 144 hours post dose (86.68%). Unchanged lorlatinib was observed as a minor component in urine, accounting for 1.1% of the renally excreted dose. While, unchanged lorlatinib comprised 5.9% of the total dose excreted in feces.

Metabolic profiling indicates that no new metabolites of lorlatinib associated with the pathway leading to the formation of PF-06895751 were identified in plasma. An additional region of early eluting radioactivity was observed in feces (~6.3% of the dose) and urine (~2.4% of the dose) but was not detected in plasma. This region is proposed to be comprised of derivatives of an intermediate metabolite, PF-06898840, the pyrido-pyrazole substructure resulting from oxidative and hydrolytic cleavage of lorlatinib.

1.2.1.2.1.4. Study B7461005

Study B7461005 is a completed Phase 1, randomized open-label study in 19 healthy volunteers to estimate the relative bioavailability of two new lorlatinib formulations (free base and maleate, [Test]) compared to the acetate solvate formulation (Reference).

The results supported the switch to free base formulation of lorlatinib in all future clinical trials including this study (see IB for more details).

1.2.1.2.1.5. Study B7461007

Study B7461007 is a completed Phase 1 study in 12 healthy volunteers, designed to estimate the absolute bioavailability of lorlatinib after oral administration of 100 mg dose relative to intravenous (IV) administration of 50 mg dose.

The absolute bioavailability of lorlatinib when administered as a single oral dose in the fasted state is 80.8% in healthy adult subjects.

1.2.1.2.1.6. Study B7461008

Study B7461008 is a completed Phase 1 study in 24 healthy volunteers, designed to evaluate the effect of rabeprazole and food on the pharmacokinetics of lorlatinib and to assess the relative bioavailability (BA) of an oral solution of lorlatinib to the tablet formulation of lorlatinib.

Results indicate that a high fat meal has no effect on the systemic exposure of lorlatinib. Similarly, proton pump inhibitor (PPI) rabeprazole had only a marginal effect on the systemic exposure of lorlatinib. Based on these results, the current recommendation is that lorlatinib can be given without regard to food or any acid reducing agents such as PPIs or H_2-receptor antagonists.

Safety data from this study recently identified asymptomatic PR prolongation. In one healthy volunteer, the PR interval prolongation was associated with one episode of transient second degree atrioventricular (AV) block (Mobitz type 1; Wenkebach). Subsequently, retrospective review of patients in the clinical study B7461001, found one patient with the PR interval prolongation that may have been associated with the progression of pre-existing AV block to complete heart block. When the complete heart block was identified, the patient was immediately evaluated and subsequently treated by placement of an implanted pacemaker.

In response to the observation of PR interval prolongation, data from all available human studies (approximately 100 patients in clinical study B7461001 and 45 in single dose healthy volunteer studies) were reviewed. Additional instances were identified of asymptomatic increases in the PR interval (>200 msec), usually most notable at the time of C_{max} (1-2 hours post-dose) in healthy volunteers. Of note, the subjects with a PR interval >200 msec were generally those with a baseline values at the upper end of the normal range.

The electrocardiogram (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 IB.

Although isolated PR interval prolongation (first or second degree AV block) may not pose an immediate risk to patient safety, the potential for development of complete heart block warrants that future studies exclude patients with a baseline PR interval ≥220 msec, or 2nd or 3rd degree AV block (unless an implanted pacemaker is in place). Further, for healthy volunteers in this study the upper limit of normal for PR interval will be defined as PR interval of 180 msec.

Additional information for this compound may be found in the SRSD, which for this study is the IB.

1.2.1.2.1.7. Study B7461011

Study B7461011 was a Phase 1 open-label, two-period, two-treatment, fixed-sequence crossover study to estimate the effect of multiple dose rifampin on a single dose of lorlatinib in healthy volunteers. The study involved the administration of a single 100-mg lorlatinib dose in the first period followed by a washout period of at least 10 days prior to the second period. The second period involved the administration of 600 mg once daily rifampin from Days 1 to 12 and a 100-mg lorlatinib single dose administration concurrently on Day 8. Twelve subjects were enrolled in the study per protocol, and all subjects completed Period 1 uneventfully. During Period 2, on Day 10 (2 days after having received the single 100-mg lorlatinib dose with 600 mg once daily [QD] rifampin) all volunteers were noted to have elevated values for AST and ALT, and the rifampin dose was withheld. No elevations in bilirubin were observed and the subjects were asymptomatic other than nausea (mild in 7 subjects, and moderate in 2 subjects) and vomiting (mild in 3 subjects and severe in 1 subject). On Day 11, the AST and ALT values were still elevated, and a decision was made to withhold the Day 11 and Day 12 rifampin doses for all subjects. Five subjects were hospitalized for observation only and discharged within 2 days; these were all reported as serious adverse events (SAEs). The elevations in AST and ALT have all trended down or normalized following the suspension of rifampin. Subjects have also been discharged from the study site, and are being followed up. The Sponsor is working to understand the possible causes for this unexpected finding, which will include the pharmacokinetic evaluation of lorlatinib, rifampin, and their metabolites.

A *Dear Investigator Letter* describing the safety observations from this study was distributed to all sites participating in lorlatinib clinical trials. The letter also reminded investigators that concomitant use of rifampin and all strong CYP3A inducers is prohibited in all lorlatinib clinical studies, as described in the exclusion criteria of the protocols, and in the 2015 and 2016 versions of the IB.

1.2.1.2.1.8. Study B7461012

Study B7461012 was a Phase 1 open-label, two-period, two-treatment, fixed-sequence crossover study to estimate the effect of multiple doses of itraconazole on a single dose of lorlatinib in healthy volunteers.

The study was designed to potentially evaluate up to 6 treatments: single dose of lorlatinib 50 mg, 75 mg or 100 mg in Period 1 and lorlatinib 50 mg, 75 mg or 100 mg on Day 5 in combination with multiple dose itraconazole 200 mg QD on Days 1 to 4 and Days 6 to 11 in Period 2, following a washout period of at least 10 days between lorlatinib doses in the two periods. Subjects were enrolled sequentially, starting with lorlatinib dosing at the lowest dose level of 50 mg. The next lorlatinib dose level was initiated only after 96 hours past lorlatinib dosing in the previous dose levels and no safety concerns were observed. A total of 16 subjects were screened, assigned to treatment, and completed the study.

Co-administration of multiple oral doses of 200 mg QD itraconazole resulted in an increase in total systemic exposure of lorlatinib (of approximately 42% for AUC_{inf} relative to a single 100 mg lorlatinib dose, given alone), indicating that metabolism of lorlatinib is sensitive to

inhibition of CYP3A enzymes. The relative increase in peak exposure (C_{max}) was 24%. Lorlatinib was well tolerated in this study, no deaths, SAEs, severe AEs, permanent discontinuations, temporary discontinuations, or dose reductions due to AEs were reported.

1.2.1.2.1.9. Study B7461016

Study B7461016 was a Phase 1, randomized, single-dose, open-label, 4-period, 4-treatment,4-sequence, crossover study balanced for first order residual effect in 20 healthy adult volunteer subjects employing administration of the Phase 2 clinical lorlatinib tablets (Reference: 4 × 25-mg tablets) and the 3 proposed commercial lorlatinib tablet strengths (Test formulations: 4 × 25-mg tablets, 2 × 50-mg tablets, 1 × 100-mg tablet) under fasted conditions.

A total of 20 subjects were screened with 5 subjects assigned to each of the 4 sequences. All subjects completed the study.

Bioequivalence was demonstrated for each of the Test formulations (lorlatinib commercial 4 × 25-mg tablets, commercial 2 × 50-mg tablets and commercial 1 × 100-mg tablet) versus the Reference (lorlatinib clinical 4 × 25-mg tablets) in healthy volunteers under fasted conditions. The 90% CIs of ratios of adjusted geometric means (Test/Reference) fell wholly within the bioequivalence limits (80%-125%) for AUC_{inf} and C_{max} for all 3 treatment comparisons. All treatments were safe and well-tolerated in healthy volunteers evaluated in this study under fasted conditions.

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

1.2.2. Study Rationale

Lorlatinib elimination occurs primarily through liver metabolism as noted in both in vitro and clinical assessments. CYP3A is one of the primary metabolizing enzymes involved in the metabolism of lorlatinib. Furthermore lorlatinib demonstrates both inhibitory and inducing effects on CYP3A. With continuous once daily dosing, the net effect of lorlatinib on its own metabolizing enzyme, CYP3A, is auto-induction at the majority of clinically tested dose levels including the RP2D of 100 mg QD. The change in liver function may potentially change the inhibitory and/or inducing potential of the liver metabolizing enzymes. Thus the effect of lorlatinib on its own metabolism in patients with hepatic impairment may differ from patients with normal hepatic function. As there may be a need to use lorlatinib to treat cancer patients who also have impaired liver function, it is important to determine the effects of hepatic impairment on the pharmacokinetics and safety of lorlatinib and also, if possible, determine whether dose modification would be necessary in these patients.

The current study is designed to primarily evaluate the effect of hepatic impairment on the steady state pharmacokinetics and safety of lorlatinib in advanced cancer patients, and if possible, provide dosing recommendations for patients with impaired liver function.

Since lorlatinib induces its own metabolism at the relevant dose levels, multiple dose lorlatinib exposures may not be predicted from single dose PK data. The potential effect of the liver dysfunction on the inhibitory and inducing effects of lorlatinib can only be seen after multiple administrations at steady-state. Hence the current hepatic impairment study will be conducted following multiple dosing with lorlatinib. Since the administration of multiple doses to healthy volunteers is precluded, the current study will be conducted in patients with solid tumors who do not have other treatment options.

The preliminary PK data from the lorlatinib clinical study B7461001 in ALK-positive NSCLC pateints showed that systemic exposure of lorlatinib is comparable in patients with mild hepatic impairment and patients with normal hepatic impairment. These results suggested a therapeutic dose of 100 mg QD (same as the current RP2D of 100 mg QD) may be tolerable in patients with mild hepatic impairment. Theoretically, liver enzyme activity may be affected by worsening liver dysfunction, thus, use of a lower starting dose of lorlatinib for patients with moderate hepatic impairment may be necessary before an appropriate dose level in this population of patients is identified. An initial dose of 50 mg QD of lorlatinib will be administered to patients with moderately impaired liver function, while, patients with mildly impaired liver function will start at the proposed fulldose of 100 mg QD of lorlatinib. Dosage modifications may be applied during the study based on the tolerability of the starting doses. Dosing patients with severe hepatic impairment will not be initiated until initial PK and safety information is available for patients with moderate hepatic impairment.

This study will permit enrolment of patients with cancer who may or may not harbor ALK or ROS1 mutations. Patients who do not harbor ALK or ROS1 mutations may not derive clinical benefit with lorlatinib, and should not have a high expectation of therapeutic benefit from lorlatinib treatment.

Providing these biospecimens is a required study activity for study sites and patients, unless prohibited by local regulations or ethics committee (EC) decision.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	Primary Endpoint(s):
• To evaluate the effect of hepatic impairment on the steady state pharmacokinetics of lorlatinib in advanced cancer patients.	• Plasma PK parameters of lorlatinib at steady state: AUC_{24} and C_{max}.
Secondary Objective(s):	**Secondary Endpoint(s):**

• To evaluate the effect of hepatic impairment on the safety of lorlatinib in advanced cancer patients.
• To evaluate the antitumor activity of lorlatinib in advanced cancer patients.
	• Type, incidence, severity, seriousness, and relationship to study medications of adverse events (AE) and any laboratory abnormalities.
	• Objective response rate (ORR).
	• Duration of response (DR).
	• Plasma PK parameters of lorlatinib, if possible:
	  • After single dose: AUC_{24}, C_{max}, AUC_{last}, T_{max}, C_{last}, and T_{last}.
	  • At steady-state: C_{min}, AUC_{last}, T_{max}, T_{last}, and CL/F.
	• Plasma PK parameters for metabolite(s) if possible: After single dose and at steady-state: AUC_{24}, AUC_{last}, C_{max}, C_{last}, T_{max}, T_{last}, $MRAUC_{24}$, $MRAUC_{last}$, and MRC_{max}.

CCI [redacted]	[redacted]
[redacted]	[redacted]

3. STUDY DESIGN

3.1. Study Overview

This will be a Phase 1, open-label, multi-center, multiple-dose, non-randomized, Phase 1 clinical trial of lorlatinib in advanced cancer patients with varying degrees of hepatic impairment and necessary age-, weight-, and gender-matched prospect normal hepatic function patients.

Patients in the study will be assigned to different groups according to their liver function. The criteria for stratification of patients based on their liver function (according to National Cancer Institute (NCI) guidance, https://ctep.cancer.gov/protocolDevelopment/docs/CTEP_Organ_Dysfunction_Protocol_Template.docx) are listed below:

Group	Groups A1 and A2	Group B	Group C	Group D
Hepatic Function	Normal	Mild impairment	Moderate impairment	Severe impairment
Total Bilirubin	≤ ULN (Upper Limit of Normal)	B1: ≤ ULN B2: >1.0 x – 1.5 x ULN	>1.5 x – 3 x ULN	>3 x ULN
AST (SGOT)	≤ ULN	B1: > ULN B2: Any	Any	Any

- Patients must fulfill both total bilirubin and AST (serum glutamic oxaloacetic transaminase [SGOT]) criteria to be included in a group.
- No distinction will be made between liver dysfunction due to metastases or liver dysfunction due to other causes.
- All liver function tests for stratification must be completed within 24 hours prior to the start of treatment.
- Group B (Mild hepatic impairment): for the purpose of this study, the "mild" liver dysfunction may be defined according to either of two criteria (Groups B_1 and B_2), so that patients in Group B may come from either of these groups. Patients in Group B_1 and B_2 are thus considered to have comparable liver dysfunction and will be combined for dose level allocation and all analysis.
- Patients whose degree of hepatic dysfunction changes (becomes worse or better) between screening and initiation of protocol therapy may be re-assigned to a different hepatic dysfunction group. This change should be discussed with the Sponsor and properly documented. Patient stratification will only be done prior to initiation of the study treatment. Patients will not be re-assigned to a different hepatic dysfunction group once treatment with lorlatinib has been started.
- Groups A1 and A2 (Normal): patients with normal liver function will be included in this study as matching control patients (Group A1 for Group B and Group A2 for Group C). If the dose for moderate hepatic impairment group (Group C) is selected to be the recommended clinical dose of 100 mg QD, the control group A2 will not be needed to be enrolled. There will be no control group designated to match severe group. However, if a decision has been made to use the same dose for severe and moderate patients, the half of the control Group A2 will be matching Group C and half will be matching Group D.

Child-Pugh scores (criteria listed in Appendix 3) will be calculated and recorded as part of the liver function testing prior to the start of the first lorlatinib dose, but will not be used to stratify patients into treatment groups.

The enrollment of approximately 76 advanced cancer patients is anticipated in this study in order to have 8 PK-evaluable patients in each of Groups A1, A2, B and C, and 6 PK-evaluable patients in Group D for final statistical analysis. Evaluable patients are those who complete the planned PK sample collection on Cycle 2 Day 1 and have no lorlatinib dose modification until completion of Cycle 2 Day 1 PK evaluation. Patients who are not evaluable for PK will be replaced.

Each patient will be treated with repeated oral once daily doses of lorlatinib in 21-day cycles until disease progression, patient refusal, or unacceptable toxicity occurs.

The planned dosing schedule for each treatment group is as follows (Table 4):

Table 4. Lorlatinib Dosing Schedule

	Group B	Group C	Group D	Group A1	Group A2
Hepatic Function	**Mild**	**Moderate**	**Severe**	**Normal**	**Normal**
Starting Lorlatinib Dose	100 mg QD	50 mg QD or otherwise determined in the first stage	determined based on preliminary safety and PK data	100 mg QD	the same dose as Group C at the second stage
Lorlatinib Dose After PK Assessment	100 mg QD	50 mg QD or otherwise determined in the first stage	determined based on preliminary safety and PK data	100 mg QD	100 mg QD

The dose schedule may be modified as necessary for individual patients according to tolerability (see Table 6 for detailed dose modification strategy).

For Group C, a two-stage enrollment will be applied.

- In the first stage, 3 PK-evaluable patients will be enrolled to receive the starting dose of 50 mg QD lorlatinib. On completion of PK sample collection through Cycle 2 Day 1 from these 3 patients, PK analysis will be performed. Upon review of the PK and tolerability of these 3 patients, a decision on dose schedule for remaining patients in the second stage will be made.

- In the second stage:
  - If it is decided to keep the planned dosing schedule (50 mg QD) for patients in Group C with moderately impaired liver function, 5 additional patients will be enrolled to have a total of 8 PK evaluable patients.
  - If a different dosing schedule is proposed for the remaining patients in Group C based on safety and PK in the first 3 subjects, then more patients will be enrolled to this group to have 8 PK evaluable patients and receive the proposed dosing schedule. The control patients in Group A2 should receive the same lorlatinib dose as proposed for the second stage in Group C until completion of PK assessment on Cycle 2 Day 1 and then switch to 100 mg QD beyond Cycle 2 Day 1. At the new dose level, the first 3 patients should be dosed one at a time with at least one week apart until some safety information at this dose level is obtained.

The enrollment for patients with severe hepatic impairment (Group D) will only be started when the dose for patients in the second stage of Group C has been determined and has been tolerated in at least one patient. The initial lorlatinib dose for Group D might be the same as the second stage Group C dose or otherwise determined by sponsor based on available preliminary safety and PK data at that time. The dosing regimen for Group D will be communicated to sites. Patients in Group D will not be matched by any control group. Initially (the first 3 patients), the patient should be dose one by one with at least 1 week apart until some safety information is obtained at the dose level.

Patients in Groups A1 (Normal hepatic function) and B (Mild hepatic impairment) will receive a starting lorlatinib dose of 100 mg (4 × 25-mg tablets) QD. The first 3 patients in in Group C (Moderate hepatic impairment) will receive a starting lorlatinib dose of 50 mg (2 × 25-mg tablets) QD. Patients in control Group A2 (Normal hepatic function) will receive the same starting lorlatinib dose as stage 2 of Group C, which could be 50 mg (2 × 25-mg tablets) QD or as otherwise determined during the second stage of Group C, and switch to 100 mg (4 × 25-mg tablets) QD after completion of PK assessment on Cycle 2 Day 1.

Enrollment into control Group A2 will only be started after the first stage for Group C has been completed and a decision on dose schedule for the stage 2 subjects in Group C has been made. Patients in control group should match patients in the respective hepatic impaired group by the following criteria:

- The mean body weight in control group will be within ±20 kg of the mean body weight of the patients in respective hepatic impaired group.
- The mean age in control group will be within ±10 years the mean age of the patients in respective hepatic impaired group.
- The gender ratio in control group will be similar (±2 patients per gender) to those in respective hepatic impaired group.

Once all the patients complete their planned PK collection, data collection for the primary objective of the study will be accomplished. After data collection for the primary objective has been completed, the sponsor could generate a study report including all PK data and other data, as defined in the Sponsor-maintained statistical analysis plan. In this case, a supplement study reported will then be generated when all patients completed the study.

4. PATIENT ELIGIBILITY CRITERIA

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

4.1. Inclusion Criteria

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

1. Females and/or male patients age ≥18 who have the capability to consent for themselves.

2. Histologically or cytologically confirmed solid malignancy or lymphoma that is metastatic or unresectable, and for which standard curative or palliative measures do not exist, or are no longer effective.

   In case of hepatocellular carcinoma, the diagnosis should be based on at least one of the following:

   a. The presence of at least one lesion, measuring ≥2 cm, with characteristic arterial enhancement and venous washout in the setting of liver cirrhosis and/or hepatitis B or C infection;

   b. The presence of liver lesion(s) (as defined in a.) with alpha-fetoprotein (AFP) ≥400 ng/mL;

   c. Tissue confirmation.

3. Biliary obstruction for whom a biliary drain or stent has been placed are eligible, provided that the drain or stent have been in place for at least 10 days prior to the first dose of lorlatinib, and the liver function has stabilized as defined by 2 measurements at least 5 days apart that put the patient in the same hepatic dysfunction stratum as defined in Section 3.1.

4. Presence of gliomas and brain metastases only if neurologically stable and treated without ongoing requirement for corticosteroids for at least 2 weeks prior to the first lorlatinib dose.

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

6. Adequate Bone Marrow Function, including:

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

    e. Platelets ≥50,000/mm^3 or ≥50 x 10^9/L;

    f. Hemoglobin ≥8 g/dL.

7. Adequate Pancreatic Function, including:

    g. Serum total amylase ≤2. 0 x upper limit of normal (ULN) without symptom of acute or chronic pancreatitis;

    h. Serum lipase ≤2.0 x ULN without symptom of acute or chronic pancreatitis.

8. Adequate Renal Function, including:

    eGFR ≥90 mL/min as calculated using the Modification of Diet in Renal Disease (MDRD) equation as follows: $eGFR\ (mL/min/1.73\ m^2) = 175 \times (S_{cr,std})^{-1.154} \times (Age)^{-0.203} \times (0.742\ if\ female) \times (1.212\ if\ African\ American)$.

9. Resolved acute effects of any prior therapy to baseline severity or Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 except for adverse events (AEs) not constituting a safety risk by investigator judgment.

10. Serum pregnancy test (for females of childbearing potential) negative at screening.

    Female patients of nonchildbearing potential must meet at least 1 of the following criteria:

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

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

11. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

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

4.2. Exclusion Criteria

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

1. Untreated esophageal varices observed on esophagogastroduodenoscopy (EGD) or imaging study; however, patients with known portal hypertension and evidence of varices on EGD or imaging study who have undergone appropriate therapy as indicated within the last 6 months (if applicable) are eligible for enrollment.

2. Uncontrolled ascites that is not stable with medical management (ie, on diuretics and salt restriction) as defined by requiring therapeutic paracentesis more than once every 4 weeks.

3. Episodes of hepatic encephalopathy within the last 4 weeks. Patients with prior episodes of hepatic encephalopathy who are clinically stable on lactulose, neomycin, and/or xifaxan therapy are allowed.

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

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, including stereotactic or partial brain irradiation. Whole brain irradiation within 4 weeks prior to randomization. Palliative radiation therapy outside of the CNS (eg bone mets) more than 48 hours prior to randomization is allowed.

7. Last anti-cancer treatment within 2 weeks prior to screening.

8. Previous high-dose chemotherapy requiring stem cell rescue.

9. Prior irradiation to >25% of the bone marrow (see Appendix 4 Bone Marrow Reserve in Adults).

10. 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.

11. Known prior or suspected severe hypersensitivity to lorlatinib or any component in lorlatinib tablet.

12. For patients who do not have liver cancer, active and clinically significant bacterial, fungal, or viral infection including hepatitis B virus (HBV) or hepatitis C virus (HCV) (eg, in case of known hepatitis B surface antigen [HBsAg] or HCV antibody positivity), known human immunodeficiency virus (HIV), or acquired immunodeficiency syndrome (AIDS)-related illness.

13. Clinically significant cardiovascular disease, that is, active or within 3 months prior to enrollment: cerebral vascular accident/stroke, myocardial infarction, unstable angina, congestive heart failure (New York Heart Association Classification Class ≥II), second-degree or third-degree AV block (unless paced) or any AV block with PR >200 msec; or

    Ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥2, uncontrolled atrial fibrillation of any grade, bradycardia defined as <50 bpm, machine-read ECG with QTc >470 msec, or congenital long QT syndrome.

14. Hypertension that cannot be controlled by medications (>150/100 mmHg despite optimal medical therapy).

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

16. 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.

17. Active hemolysis or evidence of biliary sepsis.

18. Patients who had prior major gastrointestinal surgery removing part of gastrointestinal tract (>1/3 of colon and/or any other part) and/or gall bladder.

19. Concurrent use of any of the following food or drugs (consult the sponsor if in doubt whether a food or a drug falls into any of the above categories) within 12 days prior to the first dose of lorlatinib.

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

    b. known strong CYP3A inhibitors (eg, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg, Seville oranges, pomelos], boceprevir, cobicistat, conivaptan, itraconazole, ketoconazole, posaconazole, ritonavir [alone or with danoprevir or elvitegravir or indinavir or lopinavir or paritaprevir or ombitasvir or dasabuvir or saquinavir or tipranavir], telaprevir, troleandomycin, voriconazole,). The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

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

d. known CYP3A substrates with narrow therapeutic indices (eg, alfentanil, cyclosporine, ergot alkaloid [dihydroergotamine, ergotamine], fentanyl [including transdermal patch], pimozide, quinidine, tacrolimus).

20. Prior treatment with lorlatinib.

21. Other 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 lorlatinib administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

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

23. Pregnant female patients; breastfeeding female patients; fertile male patients and female patients of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 97 days if male or 21 days if female after the last dose of lorlatinib.

24. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis or melena.

4.3. Lifestyle Requirements

4.3.1. Contraception

Lorlatinibis 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 lorlatinib is mandatory.

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

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).

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. Women 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. Approved Methods of Contraception

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

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

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

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

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

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

4.3.2. Alcohol, Caffeine, and Tobacco

- Patients must abstain from alcohol prior to enrollment in the study and continue abstaining from alcohol until collection of the final PK sample on Cycle 2 Day 1. Patients may undergo an alcohol breath test at the discretion of the investigator.

- Patients must abstain from the use of tobacco- or nicotine-containing products prior to the start of lorlatinib treatment and the collection of final pharmacokinetic sample on Cycle 2 Day 1.

- Patients are recommended to abstain from caffeine-containing products for 24 hours prior to the start of lorlatinib treatment until collection of the final pharmacokinetic sample on Cycle 2 Day 1.

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 contact list located in the study manual.

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

5. STUDY TREATMENTS

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

For this study, the investigational product(s) is lorlatinib.

5.1. Allocation to Treatment

After a patient has been shown to have a liver function within the scope of this study, provided written informed consent specifically for this protocol, completed the necessary screening assessments, and found to be eligible, the study manager (or equivalent role) will then register the patient in the study.

Once eligibility is verified, the study manager (or equivalent role) will assign enrollment numbers (provided by the Pfizer randomization Group) sequentially to eligible patients as they are screened for the study and will provide this information to the clinical site. Patients will be assigned to different groups according to their liver function (See Section 3.1 for stratification criteria).

5.2. Patient Compliance

Patients will be required to return all unused study treatment at the beginning of each cycle. The number of lorlatinib tablets returned by the patient will be counted, documented, and recorded.

A patient diary will be provided to the patients to aid in patient compliance with the dosing instructions. The diary will be maintained by the patient to include missed or changed lorlatinib doses. Patients will be required to return all bottles of lorlatinib every cycle. The number of lorlatinib tablets remaining will be documented and recorded at each cycle. The patient diary may also be used to support this part of the lorlatinib accountability process.

5.3. Lorlatinib Supplies

5.3.1. Dosage Form(s) and Packaging

Lorlatinib will be provided as tablets for oral administration. The 25-mg tablets will be supplied in separate bottles (or blister cards, as appropriate) and labeled according to local regulatory requirements.

5.3.2. Preparation and Dispensing

Lorlatinib should be dispensed at each visit per the schedule of treatment. A qualified staff member will dispense lorlatinib in the bottles (or blister cards, as appropriate) provided, in quantities appropriate for the study visit schedule. The patient/caregiver should be instructed to maintain the product in the bottle (or blister cards, as appropriate) provided throughout the course of dosing, keep lorlatinib away from children, and return the bottle (or blister cards, as appropriate) to the site at the next study visit.

5.4. Administration

All trial 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. Patients must swallow the study medication whole and must not manipulate or chew the medication prior to swallowing. A dosing card will be provided to the patients to provide guidance for the correct use of lorlatinib. Patients must be instructed that should they miss a dose or vomit any time after taking a dose, they must not “make it up” with an extra dose. Instead, resume the subsequent doses as originally prescribed. Any missed dose may be taken up to 6 hours prior to the next scheduled lorlatinib dose, otherwise it should be skipped and dosing resumed with subsequent doses as prescribed. The patient must be instructed to record all doses (including missed or vomited) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and Case Record Forms (CRFs).

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 (within 15 minutes prior to lorlatinib dosing). On ECG assessment days, the lorlatinib dose should also be taken in the clinic under the supervision of the study site personnel so that timing of assessments is appropriately synchronized.

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

Lorlatinib treatment may continue until confirmation of disease progression, patient refusal, or unacceptable toxicity despite of dose reduction or interruption, whichever occurs first.

5.5. Recommended Dose Modifications

Every effort should be made to administer lorlatinib on the planned dose and schedule.

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

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

Dose levels for lorlatinib dose modifications are provided in Table 5. All dose modifications will be reported in the CRF.

In case of adverse events, Investigators are encouraged to employ best supportive care according to local institutional clinical practices or follow the dose modification guidance for lorlatinib related adverse reactions provided in Table 6.

Table 5. Lorlatinib Dose Levels for Intrapatient Dose Modification

Dose Level	Lorlatinib Dose	Lorlatinib Dose	Lorlatinib Dose
0 (starting dose)	100 mg QD	75 mg QD	50 mg QD
-1	75 mg QD	50 mg QD	25 mg QD
-2	50 mg/QD	25 mg QD	-

Patients will be monitored closely for toxicity, and lorlatinib treatment may be adjusted by dosing interruption or reduction as indicated in Table 6. If the patient started at 100 mg QD, then dosing interruption and/or intrapatient dose reduction by 1, and if needed, 2 dose level(s) will be allowed depending on the type and severity of toxicity encountered.* If the patient started at 50 mg QD, only one dose level down (to 25 mg QD) may be allowed and should be discussed with the Sponsor based on individual benefit/risk assessment.

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

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

Table 6. Recommended Dose Modifications for lorlatinib Related Adverse Reactions

Adverse Reaction	Lorlatinib Dosing
Hypercholesterolaemia or Hypertriglyceridaemia	
Mild hypercholesterolaemia (cholesterol between ULN and 300 mg/dL or between ULN and 7.75 mmol/L) OR Moderate hypercholesterolaemia (cholesterol between 301 and 400 mg/dL or between 7.76 and 10.34 mmol/L)	Introduce or modify lipid-lowering therapy[a] in accordance with respective prescribing information; continue LORLATINIB at same dose.
Mild hypertriglyceridaemia (triglycerides between 150 and 300 mg/dL or 1.71 and 3.42 mmol/L) OR Moderate hypertriglyceridaemia (triglycerides between 301 and 500 mg/dL or 3.43 and 5.7 mmol/L)	
Severe hypercholesterolaemia (cholesterol between 401 and 500 mg/dL or between 10.35 and 12.92 mmol/L) OR Severe hypertriglyceridaemia (triglycerides between 501 and 1000 mg/dL or 5.71 and 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[a] if currently on lipid-lowering therapy, increase the dose of this therapy[a] in accordance with respective prescribing information; or change to a new lipid-lowering therapy. Continue LORLATINIB at the same dose without interruption.

Adverse Reaction	Lorlatinib Dosing
Life-threatening hypercholesterolaemia (cholesterol over 500 mg/dL or over 12.92 mmol/L) OR Life-threatening hypertriglyceridaemia (triglycerides over 1000 mg/dL or over 11.4 mmol/L)	Introduce the use of lipid-lowering therapy[a] or increase the dose of this therapy[a] in accordance with respective prescribing information or change to a new lipid-lowering therapy. Withhold lorlatinib until recovery of hypercholesterolaemia and/or hypertriglyceridaemia to moderate or mild severity grade. Re-challenge at same lorlatinib dose while maximizing lipid-lowering therapy[a] in accordance with respective prescribing information. If severe hypercholesterolaemia and/or hypertriglyceridaemia recur(s) despite maximal lipid-lowering therapy[a] in accordance with respective prescribing information, reduce lorlatinib by 1 dose level.
Central nervous system effects[b,c]	
Grade 2: Moderate OR Grade 3: Severe	Withhold dose until toxicity is less than or equal to Grade 1. Then resume lorlatinib at 1 reduced dose level.
Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue lorlatinib.
Pneumonitis	
Grade 1: Mild OR Grade 2: Moderate	Withhold lorlatinib until symptoms have returned to baseline and consider initiating corticosteroids. Resume lorlatinib at 1 reduced dose level. Permanently discontinue lorlatinib if ILD/pneumonitis recurs or fails to recover after 6 weeks of lorlatinib hold and steroid treatment.
Grade 3: Severe OR Grade 4: Life-threatening/Urgent intervention indicated	Permanently discontinue lorlatinib.
PR interval prolongation/Atrioventricular (AV) block	
First degree AV block: Asymptomatic	Continue lorlatinib at the same dose without interruption. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to heart block closely.
First degree AV block: Symptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to AV block closely. If symptoms resolve, resume lorlatinib at 1 reduced dose level.
Second degree AV block: Asymptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Monitor ECG/symptoms potentially related to heart block closely.

Adverse Reaction	Lorlatinib Dosing
	If subsequent ECG does not show second degree AV block, resume lorlatinib at 1 reduced dose level.
Second degree AV block: Symptomatic	Withhold lorlatinib. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Consider pacemaker placement if symptomatic AV block persists. If symptoms and the second degree AV block resolve or if patients revert to asymptomatic first degree AV block, resume lorlatinib at 1 reduced dose level.
Complete AV block	Withhold lorlatinib. Consider effects of concomitant medicinal products, and assess and correct electrolyte imbalance that may prolong PR interval. Refer for cardiac observation and monitoring. Pacemaker placement may be indicated for severe symptoms associated with AV block. If AV block does not resolve, placement of a permanent pacemaker may be considered. If pacemaker placed, resume lorlatinib at full dose. If no pacemaker placed, resume lorlatinib at 1 reduced dose level only when symptoms resolve and PR interval is less than 200 msec.
Other adverse reactions[c]	
Grade 1 OR Grade 2	Consider no dose modification or reduce by 1 dose level, as clinically indicated.
Greater than or equal to Grade 3	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Then resume lorlatinib at 1 reduced dose level.

ECG=electrocardiogram; HMG CoA=3-hydroxy-3-methylglutaryl coenzyme A; ULN=upper limit of normal.
[a] Lipid-lowering therapy may include: HMG CoA reductase inhibitor, nicotinic acid, fibric acid, or ethyl esters of omega-3 fatty acids.
[b] Examples of CNS effects comprise hallucination and changes in cognition, mood, mental status, or speech
[c] Grade categories are based on CTCAE classifications.

5.6. Management of Overdose

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

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

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

5.7. Lorlatinib Storage

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

Lorlatinib 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 lorlatinib 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 nonworking 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, lorlatinib must be quarantined and not used until the Pfizer provides permission to use lorlatinib. It will not be considered a protocol deviation if Pfizer approves the use of lorlatinib after the temperature excursion. Use of lorlatinib prior to Pfizer approval will be considered a protocol deviation.

Specific details regarding information the site should report for each excursion will be provided to the site.

Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions.

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

5.8. Lorlatinib Accountability

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

All bottles of study drug must be returned to the investigator by the patient at every visit and at the end of the trial.

5.8.1. Destruction of Lorlatinib Supplies

The sponsor or designee will provide guidance on the destruction of unused lorlatinib (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)

Depending on the treatment arm a patient is randomized to receive, medications specifically prohibited in the Exclusion Criteria may not be allowed during the active treatment period.

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

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

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

Medications intended solely for supportive care (eg, antiemetics, analgesics, megestrol acetate for anorexia, bisphosphonates or RANK-ligands for metastatic bone disease or osteoporosis) are allowed.

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

5.9.1. Inhibitors, Inducers and Substrates of CYP Enzymes

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 CYP3A and also an inducer of CYP3A and CYP2B6. At substantially higher concentrations than those observed clinically, lorlatinib also inhibited CYP2C9 in vitro studies.

To protect patient safety, the following cautions are provided:

- Lorlatinib metabolism may be inhibited by strong CYP3A inhibitors leading to a potential increase in lorlatinib toxicities. Coadministration of strong CYP3A inhibitors (eg, boceprevir, cobicistat, conivaptan, grapefruit juice, itraconazole, ketoconazole, lopinavir, paritaprevir and, posaconazole, ritonavir alone and with danoprevir or elvitegravir or indinavir or lopinavir or paritaprevir or ombitasvir or dasabuvir or saquinavir or tipranavir, telaprevir, troleandomycin, and voriconazole, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg, Seville oranges, pomelos]) is not recommended and alternate medications should be considered. If the concomitant use of the strong CYP3A inhibitor cannot be avoided, reduce the starting dose of lorlatinib from 100 mg orally once daily to 75 mg orally once daily. In patients who have had a dose reduction to 75 mg orally once daily due to adverse reactions and who initiate a strong CYP3A inhibitor, reduce the lorlatinib dose to 50 mg orally once daily. The patient should be closely monitored for safety and reduction of the lorlatinib dose if necessary. If concomitant use of a strong CYP3A inhibitor is discontinued, increase the lorlatinib dose (after 3 plasma half-lives of the strong CYP3A inhibitor) to the dose that was used before starting the strong inhibitor.

- Use of strong CYP3A inducers with lorlatinib is contraindicated.
lorlatinib metabolism may be induced when taking strong CYP3A inducers (eg, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's Wort) resulting in reduced plasma concentrations. Furthermore, when lorlatinib was coadministered with rifampin, increases in AST and ALT were noted. Discontinue strong CYP3A inducers for 3 plasma half-lives of the strong CYP3A inducer prior to initiating lorlatinib and until study treatment discontinuation. In addition, use with moderate CYP3A inducers (eg, bosentan, efavirenz, etravirine, modafinil) should be avoided due to the potential reduction in lorlatinib exposure.

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

- Lorlatinib induces CYP2B6 (in vitro) so concurrent use of drugs that are CYP2B6 substrates, such as bupropion and efavirenz, may have less effect. Concomitant CYP2B6 substrates 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-gp (in vitro) so concurrent use of drugs which are P-gp substrates with a narrow therapeutic index may have increased effect. The concurrent use of drugs which are P-gp substrates with narrow therapeutic index, such as digoxin is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered. If absolutely necessary to use during the study, it should be initiated following sponsor approval, and be used then with caution. The net clinical effect of lorlatinib on P-gp is currently being investigated.

The Sponsor can be contacted with questions regarding concomitant use of specific drugs.

5.9.2. Other Anti-tumor/Anti-cancer or Experimental Drugs

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

5.9.3. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to any available American Society of Clinical Oncology (ASCO) guidelines.

Patients currently being treated with a gonadotropin-releasing hormone agonist (GnRH agonist) may continue treatment while on clinical study B7461009 as long as the GnRH agonist treatment has been well tolerated for at least 3 months prior to study entry.

5.9.4. Other Prohibited Concomitant Medications and Therapies

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

- Anti-cancer systemic chemotherapy or biological therapy.
- Investigational agents other than lorlatinib.
- Radiation therapy (with the exception noted in the Concomitant Radiotherapy Section).
- Other experimental pharmaceutical products.

- Herbal remedies with anticancer properties or known to potentially interfere with major organ function or study drug metabolism (eg, hypericin).

5.9.5. Hematopoietic Growth Factors

Use of granulocyte colony stimulating factors should follow the current American Society of Clinical Oncology (ASCO) guidelines.[6] Patients who enter the study on stable doses of erythropoietin or darbepoetin may continue this treatment, and patients may start either drug during the study at the discretion of the investigator.

5.9.6. 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.

5.9.7. Concomitant Radiotherapy

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

Lorlatinib must be stopped 24 hours before and at least 24 hours after completion of radiation therapy. In view of the current lack of data about the interaction of lorlatinib with radiotherapy, lorlatinib treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment after recovery from acute radiation toxicities to baseline.

6. STUDY PROCEDURES

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

6.1. Screening

Informed Consent must be obtained prior to undergoing any study specific procedures. Informed consent for use of tissue for CCI [redacted] diagnostic development must also be obtained.

For screening procedures see the Schedule of Activities and ASSESSMENTS sections.

CCI [redacted]

CCI [redacted]

CCI [redacted]

[redacted]

6.2. Study Period

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

6.3. Follow-up

For follow-up procedures see the Schedule of Activities and ASSESSMENTS sections.

6.4. Patient Withdrawal

Withdrawal of consent:

Patients who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a patient specifically withdraws consent for any further contact with him or her or persons previously authorized by the patient to provide this information. Patients should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of lorlatinib or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the patient is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Lost to follow-up:

All reasonable efforts must be made to locate patients to determine and report their ongoing status. This includes follow-up with persons authorized by the patient as noted above. Lost to follow-up is defined by the inability to reach the patient after a minimum of 2 documented phone calls, faxes, or e-mails as well as lack of response by the patient to 1 registered mail letter. All attempts should be documented in the patient's medical records. If it is determined that the patient has died, the site will use locally permissible methods to obtain the date and cause of death. If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the patient's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff

with obtaining the patient's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the patient remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the patient's medical records.

Patients may withdraw from treatment 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 (see also the Patient Withdrawal Section) or behavioral reasons, or the inability of the patient to comply with the protocol-required schedule of study visits or procedures at a given investigator site.

Reasons for withdrawal of study treatment may include:

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

Reasons for withdrawal from study follow-up may include:

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

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

If the patient refuses further visits, the patient should continue to be followed for survival (if survival is a secondary endpoint) unless the patient withdraws consent for disclosure of future information or for further contact. In this case, no further study-specific evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

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

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

7.1. Safety Assessment

Safety assessments will include collection of AEs, SAEs, vital signs and physical examination, 12 lead ECGs, echocardiogram/multigated acquisition scan (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).

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

7.1.1. Pregnancy Testing

All pregnancy tests used in this study, either urine or serum, must have a sensitivity of at least 25 mIU/mL and must be performed by a certified laboratory. For female patients of childbearing potential, 2 negative pregnancy tests are required before receiving lorlatinib treatment (1 negative pregnancy test at screening and 1 at the baseline visit immediately before lorlatinib administration). Following a negative pregnancy test result at screening, appropriate contraception must be commenced and the second negative pregnancy test result

will then be required at the baseline visit before the patient may receive the lorlatinib treatment. In the absence of regular menstrual bleeding, the study candidate should have used 2 forms of contraception for at least 1 month before the second pregnancy test. Pregnancy tests will also be repeated at every cycle during the active treatment period, and at the end of the study to confirm that the patient has not become pregnant during the study. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period and when potential pregnancy is otherwise suspected, and may be repeated 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 patient will be withdrawn from administration of lorlatinib.

7.1.2. Adverse Events

Assessment of adverse events will include the type, incidence, severity (graded by the NCI CTCAE version 4.03) timing, seriousness, and relatedness.

7.1.3. Laboratory Safety Assessment

Hematology and blood chemistry will be drawn at the time points described in the schedule of activities and analyzed at local laboratories.

Table 7. Safety Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis§	Pregnancy Test
Hemoglobin	ALT	PT /INR	Urinalysis (including protein, glucose, occult blood as well as albumin) with reflex to microscopic. Positive protein may require additional 24-hour urine collection at the investigator's discretion.	For female patients of childbearing potential, serum or urine.
Platelets	AST	aPTT		
WBC	Alk Phos			
Absolute Neutrophils	Sodium			
Absolute Lymphocytes	Potassium			
Absolute Monocytes	Magnesium			
Absolute Eosinophils	Chloride			
Absolute Basophils	Calcium			
	Total bilirubin***			
	Direct bilirubin			
	BUN or Urea			
	Creatinine			
	Uric Acid			
Lipids	Glucose			
Total Cholesterol	Albumin			
LDL	Phosphoros or Phosphate			
HDL	Total protein			
Triglycerides	Amylase*			
Infections	Gamma glutamyl transferase (GGT)			
HBV, HCV (Screening only)	Lipase			
	Creatine kinase			
	C-reactive protein (CRP)			
	Lactate dehydrogenase (LDH)			

*** For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR, alkaline phosphatase, total bile acids and acetaminophen drug 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. To be repeated as clinically indicated.
ALT=alanine aminotransferase, aPTT=activated partial thromboplastin time, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CRP=C-reactive protein, GGT=gamma-glutamyltransferase, HBV=hepatitis B virus, HCV=hepatitis C virus, HDL=high-density lipoprotein, INR=international normalized ratio, LDH=lactate dehydrogenase, LDL=low-density lipoprotein, PT=prothrombin time, WBC=white blood cell.

7.1.4. Liver Function Assessment

Liver function will be assessed during screening and confirmed before the start of lorlatinib treatment. Liver Function Assessment should at least include tests for AST, ALT, albumin, alkaline phophatase, total bilirubin, and direct bilirubin. Tests done for blood chemistry can be used for liver function assessment. Additional tests should be performed to complete the liver function assessment if necessary. All liver function assessments for patient categorization must be completed within 24 hours prior to the start of lorlatinib treatment on Cycle 1 Day 1. Patients will be assigned to different groups according to their liver function before the start of lorlatinib treatment. Criteria for stratification based on liver function are provided in Section 3.1 of the protocol. Liver function assessments will be performed weekly until the start of Cycle 2, on Cycle 2 Day 15, on day 1 of each following cycle, at the End of Treatment, and as clinically indicated. There should be more frequent testing for liver function in case of Grade 2-4 elevations or in case of signs or symptoms consistent with hepatotoxicity or hepatic failure (eg, fatigue, weakness, anorexia, nausea, vomiting, right upper quadrant adnominal pain, jaundice, dark urine, and in rare cases, fever and rash). More frequent monitoring could be performed as the discretion of investigator at any time. Child-Pugh scores will also be calculated and recorded in conjunction with liver function tests prior to the start of the first lorlatinib dose, but will not be used to stratify patients. Liver function tests should be repeated within 48 hours if the following is observed and repeated weekly until recovery to baseline levels: If **a patient entered study with AST or ALT** baseline values within the normal range who subsequently presented with AST or ALT ≥3 × ULN concurrent with total bilirubin ≥2 × ULN, OR **a patient with baseline AST or ALT values** above the normal range who subsequently presented with AST or ALT ≥2 × the baseline values concurrent with a total bilirubin increased by ≥2 × baseline or >3 × ULN (whichever is smaller) and alkaline phosphate <2 × ULN or not available. A 4-mL serum sample obtained just prior to the first dose of lorlatinib will be stored frozen on site through completion of the study for possible use as a baseline reference should additional laboratory tests be indicated, for example, additional testing to exclude other causes of liver injury (see ADVERSE EVENT REPORTING).

7.1.5. Vital Signs and Physical Examination

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

7.1.6. (12-Lead) Electrocardiogram

A triplicate 12-lead (with a 10-second rhythm strip) tracing at supine position will be used for all ECG assessments.

All patients require a triplicate ECG measurement at screening. On treatment ECGs will be performed as outlined in the Schedule of Activity (SOA) table. At each time point requiring triplicate ECGs, 3 consecutive 12 lead ECGs will be performed approximately 2 minutes apart to determine mean QTc (average of triplicates). When they coincide with blood sample draws for PK, the ECG assessment should be performed within 15 minutes prior to a PK blood sample collection, such that the PK blood sample is collected at the planned nominal time.

Clinically significant findings seen on subsequent ECGs should be recorded as adverse events. In case of QTc >500 msec (ie, CTCAE Grade >2), ECG must be reviewed by qualified personnel at the site as soon as the finding is made, including verifying that the machine reading is accurate and that the Fridericia correction formula is applied. If the manual reading verifies a rate corrected QTc of >500 msec, repeat ECG should be immediately performed at least two times approximately 2 to 4 minutes apart.

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

Prior to concluding that an episode of prolongation of the QTc interval is due to lorlatinib, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

If a patient experiences PR interval prolongation >200 msec or second-degree or third-degree AV block, while on treatment with lorlatinib, refer to Section 5.5, Table 6.

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

If a patient experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

When matched with PK sampling, the ECG must be carried out before each PK sample drawing such that the PK sample is collected at the nominal time (ie, the timing of the PK collections over rides the timing of the ECG collections).

7.1.7. Echocardiograms/MUGA Scans

In order to monitor potential left ventricular ejection fraction (LVEF) dysfunction, 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.

7.2. Pharmacokinetics Assessments

7.2.1. Plasma for PK Analysis of Lorlatinib

Plasma samples for characterization of pharmacokinetics (PK) of lorlatinib and its metabolite(s) will be collected at the designated times listed in SOA table.

In addition to samples collected at the scheduled times, an additional blood sample may be collected from patients experiencing unexpected and/or serious AEs and the date and time of blood sample collection and of last dosing prior to PK collection documented on the CRF.

All efforts will be made to obtain the PK samples at the scheduled 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 data collection tool (eg, CRF). During the trial, actual collection times may change, but the number of samples will remain the same. If scheduled blood sample collection cannot be completed for any reason, it may be re-scheduled with agreement of the clinical investigator, patient, and sponsor.

At each designated time, blood samples (5.0 mL) to provide approximately 2.5 mL plasma (aliquoted into 2 x 2 mL tubes, approximately 1.0 mL plasma in each tube) for determination of the plasma concentrations of lorlatinib and its potential metabolite(s) will be collected into appropriately labeled tubes containing K_2EDTA. Details regarding the sample handling and shipping will be provided in the Lab Manual.

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.

PK samples will be assayed for lorlatinib and its metabolite(s) using validated analytical method(s) in compliance with Pfizer standard operating procedures (SOPs). Lorlatinib metabolite(s) to be assayed may include but not limited to PF-06895751.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), 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 deviation from the specified sample handling procedure resulting in compromised sample integrity will be considered a protocol deviation.

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7.3. Tumor Response Assessments

Tumor assessments will include all known or suspected disease sites. Imaging may include chest, abdomen and pelvis computed tomography (CT) or magnetic resonance imaging (MRI) scans; brain CT or MRI scan for patients with known or suspected brain metastases; bone scan and/or bone x-rays for patients with known or suspected bone metastases.

The same imaging technique used to characterize each identified and reported lesion at screening is preferred to be employed in the subsequent tumor assessments.

Tumor assessments will be conducted at screening (as baseline), during treatment as specified in the schedule of activities, whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 6 weeks).

Assessment of response will be made using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (see Appendix 6).

All patients' files and radiologic images must be available for source verification and for potential peer review.

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7.6. Assessment of Suicidal Ideation and Behavior

To assess suicidal ideation behaviors, the Columbia Suicide Severity Rating Scale (C-SSRS)[7] will be administered to patients at the time points described in the Schedule of Activities table. The C SSRS is a unique, simple and short method of assessing both behavior and ideation that tracks all suicidal events and provides a summary of suicidality. It assesses the lethality of attempts and other features of ideation (frequency, duration, controllability, reasons for ideation, and deterrents), all of which are significantly predictive of completed suicide.

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 lorlatinib 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 lorlatinib 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 lorlatinib (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** lorlatinib **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 patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

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

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Patient 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 patient withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

8.1.4. Time Period for Collecting AE/SAE Information

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

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

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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

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

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

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

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

8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that lorlatinib 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 lorlatinib caused the event, then the event will be handled as "related to lorlatinib" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to lorlatinib, 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 patient 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 patient 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, patient 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 patient;
- 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

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

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 patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4. Special Situations

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

- Patients 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 patients 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 patient 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.

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.

8.4.2. Exposure to the Lorlatinib During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.2.1. Exposure During Pregnancy

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

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to lorlatinib; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to lorlatinib;
    - 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 lorlatinib prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a patient or patient's partner becomes or is found to be pregnant during the patient's treatment with lorlatinib, 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 patient 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 lorlatinib.

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

8.4.2.2. 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.

8.4.2.3. 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 patient 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.

8.4.3. Medication Errors and Lack of Efficacy

Other exposures to lorlatinib under study may occur in clinical trial settings, such as medication errors and lack of efficacy.

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

*For lack of efficacy (particularly for studies conducted with vaccines, contraceptives, and products used in the treatment of life-threatening diseases or conditions [eg, anti-infectives]), see the Lack of Efficacy section below.

8.4.3.1. Medication Errors

Medication errors may result from the administration or consumption of lorlatinib by the wrong patient, or at the wrong time, or at the wrong dosage strength. Medication errors include:

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

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 medication dosing error, the sponsor should be notified immediately.

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

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

8.4.3.2. Lack of Efficacy

Lack of efficacy in an approved indication should be reported as an SAE to Pfizer Safety.

Lack of efficacy is reportable to Pfizer Safety only if 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. Analysis Sets

1. Safety analysis set:

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

2. Full analysis set:

   The full analysis set includes all enrolled patients.

3. PK analysis sets:

   The PK concentration population is defined as all enrolled patients who are treated and have at least 1 analyte concentration.

   The PK parameter analysis population is defined as all enrolled patients treated who have sufficient information to estimate at least 1 of the PK parameters of interest.

   The PK evaluable analysis population is defined as all patients in the PK parameter analysis population who have (1) completed Cycle 2 Day 1 PK collection; (2) received lorlatinib dose on Cycle 2 day 1; (3) received at least 80% of total dose within 14 days prior to Cycle 2 Day 1; (4) no dose reduction in the first cycle.

4. Response Evaluable set – includes all patients in the safety analysis population who have an adequate baseline tumor assessment.

9.2. Sample Size Determination

The sample size for this study is determined empirically based on feasibility and regulatory recommendation. Sufficient numbers of patients will be enrolled and dosed to obtain approximately 38 PK evaluable subjects (approximately 16 subjects in normal group, 8 patients each in mild and moderate groups, and 6 in severe group).

Subjects may be replaced if not PK evaluable.

9.3. Analysis of Pharmacokinetics and Pharmacodynamics

9.3.1. Analysis of Pharmacokinetics

PK analysis could be performed and PK results could be reported after all patients complete PK collection. See Section 3.1.

9.3.2. Derivation of Pharmacokinetic Parameters Prior to Analysis

Pharmacokinetic parameters will be derived from the lorlatinib and metabolite(s) concentration-time profile as described in Table 8.

Table 8. Pharmacokinetic Parameter Derivation

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	linear-log trapezoidal method
AUC_{24}	Area under the plasma concentration-time profile during one dosing interval (24 hours)	linear-log trapezoidal method
C_{max}	Maximum plasma concentration	Observed directly from data
C_{min}	Minimum plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
T_{last}	Time or C_{last}	Observed directly from the data as time of the last quantifiable concentration
CL/F	Apparent clearance	Dose/AUC_{24} at steady-state
$MRAUC_{last}$	Metabolite ratio for AUC_{last}	$(AUC_{last}/MW)_{metabolite}/(AUC_{last}/MW)_{lorlatinib}$
$MRAUC_{24}$	Metabolite ratio for AUC_{24}	$(AUC_{24}/MW)_{metabolite}/(AUC24/MW)_{lorlatinib}$
MRC_{max}	Metabolite ratio for C_{max}	$(C_{max}/MW)_{metabolite}/(C_{max}/MW)_{lorlatinib}$

MW= molecular weight; F= oral bioavailiability

Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling times will be used in the derivation of PK parameters.

9.3.3. Statistical Methods

One-way analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{last}, AUC_{24} and C_{max} at steady state for each of the hepatic impairment groups (Test) to the corresponding normal hepatic function group with the same dosing schedule (Reference). Estimates of the mean differences (Test-Reference) and corresponding 90% confidence intervals for all comparisons will be obtained from the model. The mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of geometric means (Test/Reference) and 90% confidence intervals for the ratios.

The PK parameters (defined in Table 8) C_{max}, C_{min}, AUC_{last}, AUC_{24}, T_{max}, CL/F, $MRAUC_{last}$, $MRAUC_{24}$, MRC_{max}, for lorlatinib and its metabolite(s), as appropriate, will be summarized descriptively by analyte, hepatic function group and cycle. For lorlatinib AUC_{last}, AUC_{24} and C_{max}, individual patient parameters will be plotted by hepatic function group and cycle. For AUC_{last}, AUC_{24} and C_{max} box-whisker plots of the parameters will be plotted by analyte and hepatic impairment group.

Individual concentrations in plasma will be listed and summarized descriptively by analyte, hepatic function group, cycle and nominal PK sampling time. Individual patient concentration-time data will be plotted by hepatic function group and cycle. Median profiles of the concentration-time data will be presented by hepatic function group and dose level with all hepatic function groups plotted together with separate plots for each analyte and each cycle.

For summary statistics and summary plots by sampling time, the nominal PK sampling time will be used; for individual subject plots by time, actual PK sampling time will be used.

9.4. Safety Analysis

The safety analysis population will be the primary population for evaluating patient characteristics, treatment administration, and safety.

Safety data will be reviewed on an ongoing basis during the study. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Adverse Events

Adverse Events (AEs) will be coded by system organ class (SOC) and preferred term according to Medical Dictionary for Regulatory Activities (MedDRA) terminology. AE severity will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3.

A listing of all AEs including detailed information collected for each AE (description of event, onset date/time, duration, seriousness, severity, relationship to study drug, action taken, clinical outcome) will be presented.

The number and percentage of patients who experienced any: AE, serious AE (SAE), treatment related AE, and treatment related SAE will be summarized. Emphasis in the analyses will be placed on AEs classified as treatment emergent. The analyses will summarize AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1).

Additional summaries of adverse events (AE) and of other safety data will be presented in tabular and/or graphical format and summarized descriptively, as appropriate.

Laboratory Test Abnormalities

The number and percentage of patients who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Shift tables will be provided to examine the distribution of laboratory toxicities.

For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

9.4.1. Electrocardiogram

The analysis of ECG results will be based on patients in the safety analysis set with baseline and on-treatment ECG data.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for heart rate (HR) (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 intervals, HR, RR intervals, PR intervals, QRS intervals, and QTcF (and other correction factors, eg, QTcB as appropriate) by hepatic function and dose. Individual QT (all evaluated corrections) intervals will be listed by study hepatic function, time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by hepatic function, dose and time point. For each patient and by treatment, the maximum change from baseline will be calculated as well as the maximum post-baseline interval across time-points. Categorical analysis will be conducted for the maximum change from baseline in corrected QT and the maximum post-baseline QT interval.

Shift tables will be provided for baseline vs worst on treatment corrected QT (one or more correction methods will be used) using maximum CTCAE Grade. Shift tables will also be provided for ECG abnormality at baseline vs. on treatment (yes, no, not done: (n, %)). Patients experiencing clinically relevant morphological ECG changes will be summarized (including frequency and percentage).

The effect of drug concentrations on corrected QT change from baseline may be explored graphically. Additional concentration-corrected QT analyses may be performed. Data may be pooled with other study results and/or explored further with PK/PD models. The results of such analyses will not be included in the study report.

Predose ECG on Cycle 1 Day 1 will be used as baseline for all related analysis. If the predose ECG on Cycle 1 Day 1 is not available, the ECG collected closest to Cycle 1 Day 1 (prior to the first lorlatinib dose) will be sued as baseline.

9.5. Efficacy Analysis

9.5.1. Antitumor Activity Analysis

The response-evaluable population is defined as all patients in the safety analysis population who have an adequate baseline tumor assessment. The response-evaluable population will be the primary population for evaluating clinical antitumor activity data.

Objective Response Rate (ORR) is defined as the percent of patients with complete response (CR) or partial response (PR) based on investigator evaluation, according to RECIST v1.1 (Appendix 6), relative to the response-evaluable population. Designation of best response of stable disease (SD) requires the criteria to be met at least once after the first dose of medication, at a minimum interval of 6 weeks.

Duration of response (DR) will be measured from the date that an objective tumor response (CR or PR) is first documented (whichever occurs first) to date of objective tumor progression or death due to any cause, whichever occurs first.

Descriptive statistics will be used to summarize baseline characteristics, treatment administration, and antitumor activity endpoints overall and, if applicable, separated by treatment group (as defined by hepatic function and starting dose level) and/or tumor type, as applicable. Data will also be displayed graphically, where appropriate. The ORR will be summarized along with the exact 2-sided 95% confidence interval using the exact method based on the F-distribution. DR will be summarized using Kaplan-Meier method, where appropriate.

Patients who have prior major gastrointestinal surgery removing part of the gastrointestinal tract and/or gall bladder will be excluded from descriptive summary and statistical analysis for efficacy endpoints, but will be listed for their tumor assessment.

9.6. Data Monitoring Committee

This study will not use a data monitoring committee (DMC).

For the purpose of this protocol, Sponsor procedures for periodic safety review will be applied to review individual and summary data collected in the safety and clinical databases. Procedures include:

- Surveillance for serious adverse events (SAEs) according to regulatory guidelines;
- Routine monitoring of non-serious adverse events as they are recorded in the CRFs.

Periodic teleconferences with the principal investigators on individual studies to share experiences and ensure communication.

Findings of the periodic safety reviews, according to Sponsor procedures will be documented in the project files and action taken as appropriate. Findings having immediate implication for the management of patients on study will be communicated to all principal investigators in the timeframe associated with unexpected and drug-related SAEs.

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

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

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

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

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent[/assent] 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 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 to an independent third party arranged by Pfizer.

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

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

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

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

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

12.2. Ethical Conduct of the Study

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

12.3. Patient 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 patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

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

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

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

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

The investigator must ensure that each study patient, or his or her legally acceptable representative, is fully informed about the nature and objectives of the study, 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 patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a patient's decisional capacity is so limited he or she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents

must record why the patient did not provide consent (eg, minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (eg, parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of lorlatinib, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

End of trial 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 patients and the hospital pharmacy (if applicable) within a time period set by Pfizer. 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 patient 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 (CSR 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 patients, and the CSA will control as to all other issues.

16. REFERENCES

1. Rikova K*, et al.* (2007) Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. *Cell* 131(6):1190-1203.

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3. Bergethon K*, et al.* (2012) ROS1 rearrangements define a unique molecular class of lung cancers. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 30(8):863-870.

4. Sasaki T, Rodig SJ, Chirieac LR, & Janne PA (2010) The biology and treatment of EML4-ALK non-small cell lung cancer. *European journal of cancer* 46(10):1773-1780.

5. Zou HY*, et al.* (2015) PF-06463922, an ALK/ROS1 Inhibitor, Overcomes Resistance to First and Second Generation ALK Inhibitors in Preclinical Models. *Cancer Cell* 28(1):70-81.

6. Smith TJ*, et al.* (2015) Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 33(28):3199-3212.

7. Posner K*, et al.* (2011) The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry* 168(12):1266-1277.

Appendix 1. Abbreviations

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

Abbreviation	Term
AE	adverse event
AIDS	acquired immunodeficiency syndrome
AFP	Alpha-fetoprotien
ALK	Analplastic Lymphoma Kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AV	Atrioventricular
BA	Bioavailability
BAL	bronchoalveolar lavage
BCRP	breast cancer resistance protein
CCI	[redacted]
BID	twice daily
Bpm	beats per minute
BUN	blood urea nitrogen
BNP	B-type natriuretic peptide
C_b	blood concentration
C_{eff}	effective concentration
CHF	congestive heart failure
CHO	Chinese Hamster Ovary
CK	creatine kinase
CL	Clearance
CL/F	oral clearance
CL_R	renal clearance
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
C_p	plasma concentation
CPC	Child-Pugh classification
CR	complete response
CRF	case report form
CRM	Continual Reassessment Method
CRP	C-reactive protein

Abbreviation	Term
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLI	Donor Lymphocyte Infusion
DLT	dose-limiting toxicity
DMC	data monitoring committee
CCI	[redacted]
DR	duration of response
EC	ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	external data monitoring committee
EDP	exposure during pregnancy
EEG	Electroencephalogram
EGD	esophagogastroduodenoscopy
eGFR	estimated glomerular filtration rate
EML4	echinoderm microtubule-associated protein- like 4
EOT	End of Treatment
Etc	‘and other things’ or ‘and so forth’
EU	European Union
EudraCT	European Clinical Trials Database
FOB	functional observation battery
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	Gastrointestinal
GLDH	glutamiate dehydrogenase
GnRH	gonadotropin-releasing hormone
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HLM	human liver microsome

Abbreviation	Term
hPXR	human pregnane X receptor
HR	heart rate
HRT	hormone replacement therapy
IB	investigator's brochure
IC_{50}	inhibitor concentration achieving 50% inhibition
ICH	International Conference on Harmonisation
CL	[redacted]
IND	investigational new drug
INR	international normalized ratio
IP manual	Investigational Product manual
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
LOAEL	lowest observed adverse effect level
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
MATE2K	multidrug and toxin extrusion 2K
MedDRA	Medical Dictionary for Regulatory Activities
MRAUC	metabolite ratio for AUC
MRC_{max}	Metabolite ratio for C_{max}
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
MW	molecular weight
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect-level
NOEL	Non observed effect level
NSCLC	non small cell lung cancer
OAT	Organic Anion Transporter
OATP	Organic Anion-Transporting Polypeptide
OCT	Organic Cation Transporter
ORR	Objective Response Rate
PT	prothrombin time
PCD	primary completion date
PD	pharmacodynamics
P-gp	P-glycoprotein

Abbreviation	Term
CCI	[redacted]
PI	principal investigator
PK	Pharmacokinetic(s)
PPI	proton pump inhibitor
PR	partial response
PS	performance status
PT	prothrombin time
QD	once a day
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
ROS1	c-ros oncogene 1
RP2D	recommended Phase 2 dose
R_{ss}	steady state accumulation ratio
RTK	receptor tyrosine kinases
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SOA	Schedule of Activity
SOC	system organ class
SOP	standard operating procedure
SRSD	single reference safety document
$t_{1/2}$	terminal elimination half-life
TBili	total bilirubin
TKI	tyrosine kinase inhibitor
TrkB	tropomyosin receptor kinase B
T_{max}	Time for C_{max}
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
US	United States
UVB	ultraviolet B
V	volume of distribution
V_z/F	oral volume of distribution
vs.	versus
WBC	white blood cell

Appendix 2. ECOG Performance Status

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

Appendix 3. Child-Pugh Classification (CPC) of Liver Dysfunction

CPC score is calculated from the sum of the points for each CPC criteria:

CPC Classification	Level of dysfunction	Score
A	Mild	5-6
B	Moderate	7-9
C	Severe	≥10

Assessment parameters	Assigned score for observed findings		
CPC Criteria	1	2	3
Encephalopathy grade (see table below)	0	1 or 2	3 or 4
Ascites	Absent	Asymptomatic	Requiring intervention
Serum total bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, sec prolonged	<4	4 to 6	>6

Encephalopathy Grade	Definition (electroencephalogram [EEG] required for Gr. 2,3,4)
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves on EEG
3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves on EEG
4	Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity on EEG

Appendix 4. Bone Marrow Reserve in Adults

***Adapted from R.E. ELLIS**: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961*

Marrow Distribution of the Adult

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
CRANIUM AND MANDIBLE	Head:			136.6		
	Cranium	165.8	0.75	124.3	13.1	**13.1**
	Mandible	16.4	0.75	12.3		
HUMERI, SCAPULAE, CLAVICLES	Upper Limb Girdle:			86.7		
	2 Humerus, head & neck	26.5	0.75	20.0	8.3	8.3
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
STERNUM AND RIBS	Sternum	39.0	0.6	23.4	2.3	
	Ribs:			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	**10.2**
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
	12	4.6		1.8		
PELVIC BONES	Sacrum	194.0	0.75	145.6	13.9	
	2 os coxae	310.6	0.75	233.0	22.3	**36.2**
FEMUR	2 Femoral head and neck	53.0	0.75	40.0		**3.8**

Marrow Distribution of the Adult (cont'd)

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
VERTEBRAE	Vertebrae (Cervical):			35.8		
	1	6.6	All 0.75	5.0		
	2	8.4		6.3		
	3	5.4		4.1	3.4	
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1		
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
	5	13.4		10.1	14.1	**28.4**
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
	Vertebrae (Lumbar):			114.1		
	1 pair	27.8	All 0.75	20.8		
	2	29.1		21.8	10.9	
	3	31.8		23.8		
	4	32.1		24.1		
	5	31.4		23.6		
TOTAL		**1497.7**		**1045.7**	**100.0**	**100.0**

Appendix 5. Medications with Potential PR Prolongation Effect

Please 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).

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
Disopyramide		
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 prolongation/AVB contained with Warning or Precautions sections of drug labels.
PSVT, Paroxysmal supraventricular tachycardia.

Appendix 6. RECIST Version 1.1

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);
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

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

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

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

Recording Tumor Measurements

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

The longest diameter will be recorded for each target lesion. The sum of the longest diameter for all target lesions will be calculated and recorded as the baseline sum longest diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment. All measurements should be performed using a caliper or ruler and should be recorded in metric notation in centimeters.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent."

Techniques for Assessing Measurable Disease

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

Definitions of Tumor Response

Target Lesions

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

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

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

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

Non-Target Lesions

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

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

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

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

Confirmation of Tumor Response

To be assigned a status of PR or CR, changes in tumor measurements in patients with responding tumors must be confirmed by repeat studies that should be performed ≥4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

Determination of Tumor Response by the RECIST Criteria

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

Response Evaluation Criteria in Solid Tumors

Target Lesions[1]	Non-Target Lesions[2]	New Lesions[3]	Tumor Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any response	Yes or No	PD
Any response	PD	Yes or No	PD
Any response	Any response	Yes	PD

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

Determination of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). For CR and PR, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment. It should also be noted that a tumor marker increase does not constitute adequate objective evidence of tumor progression. However, such a tumor marker increase should prompt a repeat radiographic evaluation to document whether or not objective tumor progression has occurred.

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