CLINICAL PHARMACOLOGY STUDIES

A PHASE 1, SINGLE DOSE OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETICS OF LORLATINIB IN SUBJECTS WITH IMPAIRED RENAL FUNCTION

Investigational Product Number:	PF-06463922
Investigational Product Name:	Lorlatinib
United States (US) Investigational New Drug (IND) Number:	CCI
European Clinical Trials Database (EudraCT) Number:	Not Applicable (N/A)
Protocol Number:	B7461010
Phase:	1

Document History

Document	Version Date	Summary of Changes and Rationale
Original protocol	26 March 2018	Not applicable (N/A)
Protocol Amendment 1	22 June 2018	1. In accordance with the updated FDA and Pfizer guidelines for renal impairment studies, renal function stratification will be determined by using estimated glomerular filtration rate (eGFR) as calculated using the MDRD equation, instead of CL_{cr} calculated using the Cockcroft-Gault equation. 2. The upper limit for the enrollment criterion on BMI is increased from 30.5 to 36 kg/m^2 based on site feedback of feasibility in enrolling higher body weight subjects in renally impaired groups. 3. The enrollment criterion for AST/ALT is changed from 1 x ULN to 1.5 x ULN based on site feedback of feasibility in enrolling renally impaired subjects who may have higher AST/ALT values. This is also in line with other Pfizer healthy volunteer studies. 4. The contraception requirements have been updated to require 1 form of highly effective contraception instead of 2. This is the recommendation for studies in which female subjects of child-bearing potential will not be enrolled.

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

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APPENDICES

SCHEDULE OF ACTIVITIES

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

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

Protocol Activity	**Screening**[a]	**Day -1**	**Day 1**										**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Follow-up**[q]
Hours After Dose			pre-dose	0	0.5	1	1.5	2	4	6	8	12	24	48	72	96	120	
Informed consent	X																	
CRU confinement[b]		X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X	
Inclusion/exclusion criteria	X	X																
Medical history[c]	X	X																
Physical examination[d]	X	X															X	X[q]
Safety laboratory[e]	X	X											X				X	
Demography[f]	X																	
Height	X																	
Weight	X	X																X[q]
FSH test[g]	X																	
Contraception check[h]	X	X															X	X[q]
eGFR[i]	X	X																
Urine drug testing[j]	X	X																
Triplicate ECG[k]	X	X	X			X		X	X				X				X	
Blood pressure and pulse rate[l]	X	X	X			X		X	X				X				X	X[q]
HIV, HepBsAg, HepBcAb, HCVAb testing	X																	
Lorlatinib administration[m]				X														
Pharmacokinetic blood sampling[n]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Collection[o]			X	X	→	→	→	→	→	→	→	→	→	→	→	→	X	
CCI [redacted]		X																

Protocol Activity	Screening[a]	Day -1	Day 1										Day 2	Day 3	Day 4	Day 5	Day 6	Follow-up[q]
Hours After Dose			pre-dose	0	0.5	1	1.5	2	4	6	8	12	24	48	72	96	120	
Pharmacogenomic blood sampling[p]		X																
Prior and Concomitant Medication(s)	X	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
CRU discharge																	X	
Serious and non-serious adverse event monitoring	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X

Abbreviations: →= ongoing/continuous event; BP= blood pressure; CRU = clinical research unit; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; HepBcAb = hepatitis B core antibody; HepBsAg = hepatitis B surface antigen; HCVAb = hepatitis C antibody; HIV = human immunodeficiency virus.

a. Screening should be performed within 14 days prior to the dose of lorlatinib.
b. All subjects will be admitted to the clinical research unit (CRU) on Day -1 and discharged after the last PK sample collection on Day 6.
c. Medical history will include a history of prior illegal drug, alcohol, and tobacco uses. Medical history will be recorded on screening and updated on Day -1.
d. A full physical exam (PE) will be performed by trained medical personnel at the investigator site at screening or at Day -1. A limited PE may be performed at other designated time points at the discretion of the investigator.
e. Clinical safety laboratory tests will be performed following an overnight fast and will include hematology, clinical chemistry, and urinalysis.
f. Demographics will include subject race, ethnicity, date of birth, age, and gender during the screening visit.
g. For postmenopausal (amenorrheic for at least 12 consecutive months) female subjects only.
h. On screening, Day -1 and discharge day, and during follow-up visit if performed, the investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the contraception guidelines.
i. Subjects will need to demonstrate stable renal function during the screening period within approximately a 2-week timeframe prior to dosing. Stable renal function is defined as 2 eGFR values [calculated using the Modification of Diet in Renal Disease (MDRD) equation] obtained at least 3 days but not more than 14 days apart being within 25% of each other. The average value of the 2 eGFR values will be used for enrollment and initial renal function stratification. The SCr value used to calculate eGFR collected within 24 hours prior to lorlatinib dosing will be used for final subject stratification, group assignment, and PK analysis. The CL_{cr} value on Day -1 (calculated by Cockcroft-Gault equation) will also be calculated and recorded.
j. Urine drug (mandatory) and alcohol breath test (at the discretion of the investigator) will be performed at screening and on Day -1. These tests may be performed at any other time at the discretion of the investigator.
k. Triplicate 12-lead ECG readings, approximately 2 minutes apart, will be taken at times specified in the table. All ECG assessments will be made after at least a 10-minute rest in a supine position and prior to any blood draws or vital sign measurements.
l. Single supine blood pressure and pulse rate measurements will be performed following at least a 5-minute rest in a supine position. BP and PR assessments will be performed after the collection of ECGs and prior to the collection of blood draws if scheduled at the same time.
m. On Day 1, a single oral dose of lorlatinib will be administered in the fasted state as directed. The time of lorlatinib administration will be designated as time 0.
n. Serial PK blood samples will be collected prior to lorlatinib dose (time 0) and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), and 120 (Day 6) hours post dosing.

o. Total urine collection will be performed on all subjects. A blank urine sample of at least 50 mL will be collected prior to lorlatinib administration. Post-dose urine collection will be separated into 0-24, 24-48, 48-72, 72-96, and 96-120 hour intervals.

p. CCI one 4 mL blood sample for Pharmacogenomics should be drawn on Day -1. If not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a subject visit.

q. Follow-up activities (if necessary) will be performed at the discretion of the principal investigator, if there is an unresolved AE(s) at discharge, or in case of an early withdrawal. These activities may include, but are not limited to, limited PE and weight, contraception check, and supine BP and pulse rate, adverse events, and concomitant medications. Follow-up contact will be completed at least 28 calendar days after the last administration of the investigational product to capture any potential adverse events.

Pharmacokinetic Sampling and ECG Collection Schema

Study Day(s)	**1**										**2**	**3**	**4**	**5**	**6**
Hours Before/After Dose	**Pre-dose[a]**	**0**	**0.5**	**1**	**1.5**	**2**	**4**	**6**	**8**	**12**	**24**	**48**	**72**	**96**	**120**
Study treatment administration		X													
PK blood sampling	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate ECG[b]	X			X		X	X				X				X
Urine Collection[c]	X	X	→	→	→	→	→	→	→	→	→	→	→	→	X

Abbreviation: PK = pharmacokinetic.

a. Pre-dose sample collection.

b. Triplicate 12-lead ECG readings, approximately 2-4 minutes apart, will be taken at times specified in the table. All ECG assessments will be made after at least a 10-minute rest in a supine position and prior to any blood draws or vital sign measurements.

c. Total urine collection will be performed on all subjects that produce urine. A blank urine sample of at least 50 mL will be collected prior to lorlatinib administration. Post-dose urine collection will be separated into 0-24, 24-48, 48-72, 72-96, and 96-120 hour intervals.

1. INTRODUCTION

1.1. Mechanism of Action/Indication

Lorlatinib, also known as PF-06463922, is a selective, adenosine triphosphate (ATP) competitive small molecule tyrosine kinase inhibitor (TKI) of the Anaplastic Lymphoma Kinase (ALK) or c-ROS oncogene 1 (ROS1) 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 advanced ALK-positive non-small-cell lung carcinoma (NSCLC) or ROS1-positive NSCLC.

1.2. 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% 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. 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 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 efficacious concentration (C_{eff}) (total) of 7.6 ng/mL, 62 ng/mL, and 150 ng/mL, respectively.

1.3. Non Clinical Pharmacokinetics, Metabolism and Safety of Lorlatinib

The single-dose pharmacokinetics (PK) of lorlatinib was evaluated in nonclinical species following intravenous (IV) and oral administration. Plasma clearance (CL) in rats and dogs were 16 mL/min/kg and 9 mL/min/kg, respectively. Lorlatinib was rapidly 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. Systemic exposures (peak concentration [C_{max}] and area under the concentration-time curve [AUC]) to lorlatinib increased with increasing dose in an approximately proportional manner

in the pivotal toxicology studies in rats (up to 30 mg/kg/day) and dogs (up to 25 mg/kg/day). The binding of lorlatinib to plasma proteins were 70%, 71%, and 66% for rat, dog, and human, respectively. The mean whole blood to plasma concentration ratios (Cb/Cp) of lorlatinib in mouse, rat, rabbit, dog and human were 0.776, 0.838, 1.05, 0.809 and 0.985, respectively. After oral administration of a 10 mg/kg dose of lorlatinib to male rats, the free (unbound) AUC ratios of unbound brain/plasma and cerebrospinal fluid (CSF)/plasma were approximately 0.25 and 0.37, respectively. This data from preliminary study indicates that lorlatinib can cross the blood brain barrier.

Contribution of individual cytochrome P450 (CYP) enzymes and non-CYP enzymes to lorlatinib metabolism was tested in-vitro using human hepatocytes, human liver microsomes (HLM), and recombinant enzymes. Lorlatinib was metabolized primarily by CYP3A4 and UGT1A4, with minor contributions from CYP2C8, CYP2C19, CYP3A5, and UGT1A3.

The potential for lorlatinib (0.1 to 100 μM) to inhibit human CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 enzymes was investigated in human liver microsomes (HLM). The 50% inhibitory concentration [IC_{50}] values of lorlatinib for the direct inhibition of CYP1A2, 2B6, 2C8, 2C19, 2D6 were >100 μM. The IC_{50} value for the direct inhibition of CYP2C9 was 44 μM. The IC_{50} values for the direct inhibition CYP3A measured by inhibition of testosterone 6β-hydroxylase, midazolam 1′-hydroxylase, and nifedipine oxidase activities were 23, 10, and 22 μM, respectively.

In vitro assessment utilizing HLM indicate that lorlatinib has a low potential to inhibit UGT1A1, 1A4, 1A6, 1A9, 2B7, and 2B15 at clinically relevant concentrations.

Studies addressing the potential for lorlatinib to inhibit intestinal, hepatic, and renal transporters were carried out. Lorlatinib did inhibit digoxin efflux, in in-vitro Madin Darby canine kidney with multidrug resistance protein 1(MDCK-MDR1) cells, with an IC_{50} value of 3 μM, indicating that that lorlatinib may have the potential to inhibit P-glycoprotein (P-gp). Lorlatinib has a low potential for drug-drug-interaction (DDI) with compounds that are substrates of OATP1B1 and 1B3 at clinically relevant concentrations. Lorlatinib did not inhibit OAT1 and OCT2 (IC_{50} >50 μM), but did inhibit OAT3 with an IC_{50} value of 2.7 μM. This data suggest that lorlatinib may have the potential to inhibit OAT3 at clinically relevant concentrations.

Time-dependent inhibition of CYP1A2, 2B6, 2C8, 2C9, 2C19, or 2D6 enzymes was not observed after preincubation with lorlatinib in the absence or presence of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH), as evidenced by the absence of a shift in the IC_{50} values. Lorlatinib demonstrated time-dependent inhibition of CYP3A as IC_{50} values shifted approximately 28, 14, and 25-fold to 0.81, 0.74, and 0.87 μM for testosterone 6β-hydroxylase, midazolam 1′-hydroxylase, and nifedipine oxidase activities, respectively, after preincubation with NADPH. Additional evaluations in HLM and hepatocytes using midazolam and testosterone as marker substrates confirmed that lorlatinib is a time-dependent inhibitor of CYP3A.

Induction of CYP1A2, 2B6, and 3A4 by lorlatinib (0.03 to 125 μM) was assessed in human cryopreserved hepatocytes from 3 donors and compared with induction by the positive controls, omeprazole, phenobarbital, and rifampin, respectively. CYP1A2 messenger ribonucleic acid (mRNA) levels and activity was not induced by lorlatinib at concentrations up to 30 μM. Lorlatinib did induce mRNA levels and the activity of CYP2B6 and CYP3A4 at concentrations ≥0.5 μM and ≥0.1 μM, respectively.

Lorlatinib was evaluated in genetic toxicology assays consisting of definitive bacterial reverse mutation, in vitro micronucleus, and in vivo rat micronucleus assays. In addition, an assessment of centromere staining was included as part of an exploratory in vitro micronucleus assay. Lorlatinib was not mutagenic when tested in the bacterial reverse mutation assay at up to 5000 μg/plate with or without metabolic activation. In the in vitro micronucleus assay in human TK6 lymphoblastoid cells, lorlatinib was associated with a statistically significant increase in micronuclei formation in the 4-hour treatment conditions with and without metabolic activation. Lorlatinib was negative for inducing micronuclei in the 27-hour treatment without metabolic activation up to the highest evaluated concentration (142 μM; based on cytotoxicity). Lorlatinib was also positive in the in vivo (rat) micronucleus assessment at 100 mg/kg/day. A no observed effect level (NOEL) of 30 mg/kg/day was identified with associated unbound area under the concentration-time curve from time 0 to 24 hours (AUC_{24}) up to 54,000 ng•h/mL and unbound C_{max} up to 3010 ng/mL (female rats) with a projected human safety margin of ≥20 times (unbound C_{max} exposure of 167 ng/mL and area under the concentration-time curve from time 0 extrapolated to time infinity (AUC_{inf}) exposure of 2594 ng•h/mL for a single 100 mg human dose). Centromere staining of micronucleated cells using fluorescent in situ hybridization (FISH) analysis was demonstrated in micronucleated TK6 cells and provides strong evidence for an aneugenic mechanism. Based on the lack of direct deoxyribonucleic acid (DNA) interaction and the projected safety margin for aneugenic activity, genetic toxicity risks to humans after a single 100 mg dose of lorlatinib is considered to be minimal.

Lorlatinib was well-tolerated in rats (male) and dogs given up to 100 mg/kg as a single dose. Minimal degeneration of pancreatic islet cells was observed in rats after a single dose at 100 mg/kg. Systemic unbound AUC_{24} exposures at 100 mg/kg in rats and dogs after the single dose were 4212 and 16,849 ng•h/mL, respectively, with a projected human safety margin of 6.5× (unbound AUC_{inf} exposure of 2594 ng•h/mL for a single 100 mg human dose). In 1-month repeated-dose nonclinical toxicity studies conducted with lorlatinib, the primary target organ findings were observed as effects on the pancreas, liver, hematopoietic and cardiovascular systems, and peripheral nerve of the rat and/or dog following single repeat doses. Additional findings identified in the rat or dog included an effect on the testis and epididymis, cognition and neurological function, gastrointestinal system, and skin. Findings of uncertain risk to humans included a non-specific inflammatory response, and effects on the thymus and clinical chemistry parameters related to the kidney. Lorlatinib also has the potential to be a phototoxicant. For additional information on repeat-dose nonclinical study findings refer to the single reference safety document [SRSD], which is the Investigator's Brochure (IB) for lorlatinib.

Lorlatinib was assessed in a series of safety pharmacology studies for potential effects on cardiovascular, central nervous system, and pulmonary function. Given that lorlatinib is a central nervous system (CNS) penetrable compound and a potent inhibitor of TrkB receptors that have been implicated in synaptic plasticity, long-term potentiation, and memory processes, additional ex vivo and in vivo assessments were included as part of the safety pharmacology package to evaluate the potential to cause cognitive deficits. Lorlatinib was evaluated for its effect on the human ether-a-go-go related gene (hERG) potassium channel, stably expressed in Chinese Hamster Ovary (CHO) cells. The IC_{50} value for hERG current inhibition is >100 μM (>40,641 ng/mL). As such, it is considered unlikely for lorlatinib to cause QT prolongation after a single human dose of 100 mg (unbound C_{max} exposure of 167 ng/mL). An in vivo cardiovascular assessment was performed following administration of a single dose in a telemetered rat study. Dose-dependent increases in blood pressure (systolic, diastolic, and mean) compared to vehicle control were observed at all doses tested with maximal increases (22 and 37 mm Hg at 10 and 30 mg/kg, respectively) observed 2-3 hours post-dose. Effects started immediately post-dose and continued for up to 21 hours post-dose. A biphasic heart rate response was also observed at 10 and 30 mg/kg, with an initial decrease during the first 2 hours post-dose and a subsequent increase at 12 or 15 hours post-dose that continued to 21 hours post-dose. The maximal decrease in heart rate was 36 beats per minute (bpm) and the maximal increase was 31 bpm. The unbound C_{max} associated with cardiovascular changes at 10 mg/kg/day is projected to be 623 ng/mL, based on a single-dose rat toxicity study, approximately 4 times the unbound C_{max} projected at a single human dose of 100 mg (167 ng/mL). Additional cardiovascular findings were observed following repeat dose cardiovascular assessments in rats and dogs, and are summarized in the SRSD.

To evaluate potential effects on the central nervous system, a functional observation battery (FOB) was incorporated into a 14-day repeat-dose and 1-month toxicity study in rats. FOB effects were primarily observed in moribund animals at 60 mg/kg/day following 3 and 13 days of dosing, including abnormal behavior (noted as teeth chattering), involuntary movements (noted as retropulsion and trembling), abnormal gait, uncoordinated air righting reflex, and reduced extensor thrust response. There were no FOB changes identified following 1 month of dosing in the definitive rat study at comparable C_{max} exposures achieved at the highest dose tested (30 mg/kg/day); therefore, it is not clear if the observations were directly due to effects on the CNS or related to morbidity. The CNS effects at 60 mg/kg/day were associated with Day 14 unbound C_{max} values of ≥1926 ng/mL that are approximately 12 times the unbound C_{max} projected after a single human dose of 100 mg (167 ng/mL). The potential for an effect on cognitive function was suggested from an ex vivo hippocampal brain slice assay and an exploratory in vivo model, the rat contextual renewal model. Lorlatinib caused a significant reduction in amplitude of long term potentiation, a measure that is widely considered as one of the cellular mechanisms that underlie learning and memory formation. This effect was observed at 1 μM (406 ng/mL) but not at 100 nM (41 ng/mL). As TrkB receptors have been implicated in synaptic plasticity, long term potentiation, as well as memory processes in rats, the results with lorlatinib may reflect a potential to affect cognitive function that is driven by secondary pharmacology at the TrkB receptor; however, these results cannot be used to assess safety margins relevant to human exposure due to the exploratory nature and variability in sensitivity of the model.

Range-finding developmental toxicity studies were conducted in rats and rabbits. Embryonic and fetal toxicity (including embryo lethality and fewer and smaller viable fetuses with some external and visceral malformations) was observed in both species at all dose levels, with the lowest observed adverse effect level (LOAEL) of 1 and 4 mg/kg/day in rats and rabbits, respectively with unbound AUC_{24} exposures of 2315 and 1138 ng•h/mL, respectively. The projected human safety margins were determined to be 1 times and 0.4 times in rats and rabbits, respectively (unbound AUC_{inf} of 2594 ng•h/mL at a single dose of 100 mg in humans).

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

1.3.1. Clinical Summary

1.3.1.1. Safety and Pharmacokinetics

There are 3 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 open-label, dose finding study to evaluate safety, efficacy, pharmacokinetics and pharmacodynamics of avelumab [MSB0010718C] in combination with either crizotinib or lorlatinib in patients with advanced or metastatic NSCLC. B7461006 is an open-label, multicenter, randomized Phase 3 study comparing lorlatinib to crizotinib in treatment-naïve ALK-positive advanced NSCLC.

Eight (8) healthy volunteer studies that have been completed are described in detail below and include B7461004, B7461017, B7461005, B7461007, B7461008, B7461011, B7461012, and B7461016. These studies also utilized the recommended Phase 2 dose (RP2D) of 100 mg once daily (QD) for a single dose administration. B7461004 and B7461017 are completed radio-labelled mass balance studies. B7461005 is a completed relative bioavailability study. B7461007 is a completed absolute bioavailability study. B7461008 is a completed study that evaluated the effects of acid-reducing agents and food on PK of lorlatinib. B7461011 is a completed study that 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.

1.3.1.1.1. 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 advanced ALK-positive and advanced ROS1-positive 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 advanced ALK-positive or advanced ROS1-positive NSCLC with or without asymptomatic 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 advanced ALK-positive NSCLC and patients with advanced ROS1-positive 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 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 May 2016, 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 68.5 % patients, CNS EFFECTS reported in 44.4% of patients, HYPERTRIGLYCERIDEMIA and peripheral edema reported each in 37.0% of patients, and PERIPHERAL NEUROPATHY reported in 35.2% of the patients. All of the treatment-related AEs were reported with a maximum Common Terminology Criteria (CTC) Grade 3, with the exception of 2 patients with Grade 4 HYPERCHOLESTEROLEMIA and 1 patient with Grade 4 gamma-glutamyltransferase increased. Of note, terms in all caps are cluster terms as defined in the IB.

The Phase 2 began enrollment in September 2015. Enrollment has been rapid, with 111 patients dosed as of May 2016. 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)
V_z/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)			

Source: B7461001 CSR Table 14.4.4.1.1.1

Geometric mean (geometric %CV) for all except: median (range) for T_{max}; arithmetic mean (± standard deviation) 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.

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 (± standard deviation) 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 CCI 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, apparent oral clearance (CL/F) of 9.8 to 15.8 L/hr and 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 single dose terminal elimination half-life. The observed and steady state accumulation ratios (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 significant at higher dose level, as the observed accumulation index becomes smaller while the predicted accumulation index stays similar with increase of dose.

PK data (March 2017) after 100 mg single and multiple dosing in Phase 1 with CCI drug form and in Phase 2 with CCI 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)	$t_{½}$ (hr)	CL/F (L/hr)	V_z/F (L)
Phase 1: CCI	**Formulation**						
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 (1.00-4.00)	NA	19.52 (30)	NA
Phase 2: CCI	**Formulation**						
Single Dose	19	9088 (35)	695.2 (40)	1.15 (0.500-4.02)	23.6 ± 9.37	11.01 (35)	351.5 (37)
Multiple Doses	22	5650 (39)	576.5 (42)	1.96 (0.500-22.7)	NA	17.70 (39)	NA

Source: B7461001 CSR, Table 14.4.4.1.2.1.
Geometric mean (%CV) for AUC, C_{max}, CL/F, and V_z/F; arithmetic mean (± standard deviation) for $t_{½}$; 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 × 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 area under the concentration-time curve from time 0 to the time of the last quantifiable concentration (AUC_{last}) geometric mean values (coefficient of variation [%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 medications which are either sensitive CYP3A substrates or substrates with narrow therapeutic indices should be avoided.

1.3.1.1.2. Study B7461004 and Study B7461017

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

Results indicated a mean 47.7% radioactivity recovery in urine and 40.9% recovery in feces through the last collection interval. Most of the administered radioactivity was recovered in the first 144 hours post-dose (85.11%). The overall mean recovery of radioactivity in urine and feces samples was 88.6% 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 indicated that the most abundant 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.

Study B7461017 is a second absorption, distribution, metabolism, excretion (ADME) study with 100 μCi/100 mg [^{14}C]lorlatinib conducted in 6 healthy male volunteers that has completed as of January 2018 and the analyses of the results are still ongoing. The objective of this study was to further the understanding of human metabolism of lorlatinib, specifically with respect to the metabolic pathway involving the formation of PF-06895751, a benzoic acid metabolite identified in Study B7461004 as the major lorlatinib metabolite in plasma, and the metabolic fate of the resultant "bottom half" of the lorlatinib molecule. For this purpose, the location of the radiolabel was moved from the original location on the carbonyl carbon (B7461004) to the pyrazole ring (B7461017). Additional objectives included: the evaluation of the PK of lorlatinib and its PF-06895751 metabolite, evaluation of the differences in total radioactivity profile resulting from the change in the location of the radiolabel on the lorlatinib molecule, as well as confirmation of mass balance and the relative contributions from urinary and fecal routes of excretion with the change in radiolabel location.

Metabolic profiling analysis in plasma, urine and feces from Study B7461017 is still currently ongoing. However, based on preliminary data it is not anticipated that there will be a meaningful change in the identification of the drug metabolizing enzymes contributing to the metabolic clearance of lorlatinib. There are no new metabolites identified with abundance greater than or close to that of PF-06895751.

1.3.1.1.3. 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 (CCI [redacted], [Test]) compared to the CCI [redacted] formulation (Reference).

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

1.3.1.1.4. 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 relative to intravenous (IV) administration.

The results of this study indicated that the absolute bioavailability of lorlatinib when administered as single oral dose in the fasted state was 80.78% in humans.

1.3.1.1.5. 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.

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 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 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 the healthy volunteers in this study the upper limit of normal for PR interval will be defined as PR interval of 180 msec.

1.3.1.1.6. Study B7461011

Study B7461011 was a Phase 1 open-label, two-period, two-treatment, fixed-sequence crossover study to estimate the effect of multiple doses of 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. During Period 2, on Day 10 (2 days after having received the single 100-mg lorlatinib dose with 600 mg QD rifampin) all volunteers were noted to have elevated values for aspartate aminotransferase (AST) and alanine aminotransferase (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 (5) subjects were hospitalized for observation and these events were reported as serious adverse events (SAEs). The subjects were subsequently discharged within 2 days and with no further clinical sequelae. The elevations in AST and ALT trended down or normalized following the suspension of rifampin.

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.

1.3.1.1.7. 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 2 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.

1.3.1.1.8. 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.

1.4. Study Rationale

In humans, unchanged lorlatinib accounted for less than 1% of dose in urine, indicating minimal urinary excretion of parent drug in humans. Therefore, renal impairment would not be expected to have a major effect on lorlatinib PK. A population PK analysis was conducted with data from 95 healthy volunteers from 6 healthy volunteer studies (B7461004,

B7461005, B7461007, B7461008, B7461011 and B7461016) and 330 ALK-positive or ROS1-positive NSCLC patients from the B7461001 clinical study (PMAR-EQDD-B746a-DP4-681). Baseline renal function was evaluated in the model as a potential covariate for lorlatinib PK. The analysis population for single dose PK included 226 healthy volunteers and patients with baseline normal renal function (defined as creatinine clearance [CL_{cr}] ≥90 mL/min), 120 with mild renal impairment (defined as CL_{cr} ≥60 mL/min and CL_{cr} <90 mL/min), 45 with moderate renal impairment (defined as CL_{cr} ≥30 mL/min and CL_{cr} <60 mL/min), and 1 patient with severe renal impairment (defined as CL_{cr} <30 mL/min). Baseline creatinine clearance was determined to be a statistically significant predictor of lorlatinib clearance in the covariate analysis. The median estimated single dose lorlatinib clearance was 18% and 26% lower in mild and moderate renal impairment (8.04 L/hr and 7.22 L/hr), respectively, compared to those with baseline normal renal function (9.80 L/hr), suggesting potentially higher exposure in the impaired subpopulations. Despite the estimated decrease in median lorlatinib clearance, the range of individual estimates of lorlatinib clearance for patients with mild and moderate renal impairment heavily overlapped with the range estimated for those with normal renal function. No conclusions could be drawn for patients with severe renal impairment due to the small sample size (n=1). As a result of this analysis, this present study is being conducted to evaluate the greatest potential effect of varying extent of renal impairment (ie, mild, moderate, and severe) on lorlatinib PK with single dose administration.

In this study, the PK of lorlatinib after a single oral dose of lorlatinib will be evaluated in non-cancer subjects with normal renal function, mild renal impairment, moderate renal impairment (defined as estimated glomerular filtration rate [eGFR] ≥30 mL/min and eGFR <60 mL/min), and severe renal impairment (defined as eGFR <30 mL/min not requiring dialysis) who are otherwise healthy. Data from this study would allow for the estimation of any changes in lorlatinib plasma exposure with varying extent of renal impairment.

1.5. Dose Rationale

As discussed in Section 1.3, lorlatinib was evaluated in a series of in vitro and in vivo genetic toxicity studies. The no effect level for micronucleus induction was identified at 30 mg/kg/day, and is associated with unbound AUC_{24} exposures up to 54,000 ng•h/mL (female rats), offering a safety margin 7 times over the total AUC_{inf} observed (7629 ng•h/mL

for CCI tablets, Study B7461005) from a single oral dose of 100 mg in humans. Based on the lack of direct DNA interaction and the expected safety margin for aneugenic activity, genetic toxicity risks to humans after a single 100 mg dose of lorlatinib is considered to be minimal.

The recommended Phase 2 dose for lorlatinib is 100 mg QD, which, in the Phase 1 dose-escalation portion of Study B7461001, was well-tolerated and associated with antitumor activity. It is two dose levels below the dose (and 50% of the dose) at which a DLT was observed: 200 mg QD. MTD was not reached for lorlatinib with highest clinically tested dose being 200 mg QD. Lorlatinib 100 mg single-dose administered as a single agent was demonstrated to be safe and well-tolerated in healthy volunteer studies. As tested in cancer patients, single doses of lorlatinib up to 200 mg have been safely administered and there is a large safety margin based on preclinical and clinical data. Hence, potential increases in lorlatinib exposure that may be observed with renal impairment should be safe for up to a 2-fold increase from the proposed 100 mg single dose. The 18% decrease in clearance and resultant exposure increase following a single 100 mg dose of lorlatinib in mild renal impairment NSCLC patients from Study B7461001 (as described in Section 1.4) is expected to be below the 2-fold threshold of exposure known to be safe and well-tolerated for single dose administration. To be conservative, subjects with varying degrees of renal impairment will not be dosed simultaneously, but rather enrollment will occur sequentially starting first with the subjects with mild renal impairment, then the subjects with moderate renal impairment, and finally the subjects with severe renal impairment. Enrollment in each group will initiate only until safety data from the prior less severe renal impairment population is first characterized. This present study will evaluate the 100 mg single dose of lorlatinib first in mild and moderate renal impairment subjects. Based on the initial PK, safety, and tolerability data from the prior less severe renal impairment population(s), dose reduction may be adopted for subjects with more severe renal impairment as determined by the Sponsor and in Section 3.1.

2. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective(s):	**Primary Endpoint(s):**
• To evaluate the effect of renal impairment on the single dose pharmacokinetics of lorlatinib on otherwise healthy subjects.	• Plasma AUC_{inf} and C_{max} for lorlatinib.
Secondary Objective(s):	**Secondary Endpoint(s):**
• To evaluate the safety and tolerability of a single dose of lorlatinib in healthy subjects and subjects with renal impairment.	• Clinical laboratory tests, physical examination findings, vital sign measurements, ECGs, and adverse events.
Tertiary Objective(s):	**Tertiary Endpoint(s):**
• To evaluate the pharmacokinetics of lorlatinib metabolite(s) in healthy subjects and subjects with renal impairment who are otherwise healthy.	• Plasma AUC_{last}, T_{max}, $t_{½}$, CL/F, V_z/F, CL_R, Ae and Ae% for lorlatinib. • Plasma AUC_{inf}, AUC_{last}, C_{max}, T_{max}, $t_{½}$, MRC_{max}, $MRAUC_{inf}$, $MRAUC_{last}$ for lorlatinib metabolite(s).

Exploratory Objective(s):	Exploratory Endpoint(s):
[redacted]	[redacted]

3. STUDY DESIGN

3.1. Study Overview

This will be a Phase 1, open-label, multi-center, single treatment study in subjects with normal renal function and varying degrees of renal impairment. Each subject will receive a single oral dose of lorlatinib administered in the fasted state.

This study is aimed toward enrolling approximately 32 evaluable subjects who complete the PK assessments. Subjects with the following renal function will be enrolled (Table 4).

Table 4. Renal Function Groups

Group (n)	Renal Function	eGFR
A (n=8)	normal	≥90 mL/min
B (n=8)	mild renal impairment	≥60 - <90 mL/min
C (n=8)	moderate renal impairment	≥30 - <60 mL/min
D (n=8)	severe renal impairment	<30 mL/min and not requiring dialysis

Subjects who do not complete all PK collections may be replaced to ensure 8 evaluable subjects in Groups A, B, and C and at least 4 evaluable subjects in Group D.

eGFR will be calculated using the Modification of Diet in Renal Disease (MDRD) equation as follows:

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 175 \times (S_{cr,\,std})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$$

where $S_{cr,\,std}$ denotes serum creatinine measured with a standardized assay for serum creatinine. Note that the value of eGFR, which is directly obtained from the lab or calculated using the equation above, is generally normalized to an average body size of 1.73 m^2 for diagnosis, prognosis and treatment of renal disease. In terms of clearance of renally filtrated drugs (including secreted drugs), renal elimination capacity is related to absolute glomerular filtration rate (GFR) in mL/min. The MDRD-derived, body surface area (BSA)-adjusted value of eGFR used to obtain absolute GFR (mL/min) for renal disease classification or subject assignment into different renal disease groups should be multiplied by the individual subject's normalized body surface area (ie, measured BSA/1.73 m^2). The BSA of an individual can be calculated by the following formula as described below:

$$BSA = (Weight^{0.425} \; x \; Height^{0.725}) \text{ x } 0.007184$$

In addition CL_{cr} will be calculated using the Cockcroft-Gault equation as follows:

$$CL_{cr}\ (mL/min) = \frac{[140 - age\ (years)] \times total\ body\ weight\ (kg) \times (0.85\ for\ females)}{72 \times serum\ creatinine\ (mg/dL)}$$

Subjects will need to demonstrate stable renal function during the screening period within approximately a 2-week timeframe prior to dosing. Stable renal function is defined as 2 eGFR values obtained at least 3 days but not more than 14 days apart being within 25% of each other. The average value of the 2 eGFR values will be used for study enrollment and initial renal function stratification. The SCr value used to calculate eGFR collected within 24 hours prior to lorlatinib dosing will be the value used for final subject stratification, group assignment, and PK analysis. The CL_{cr} value will be recorded at the same time eGFR is determined. The CL_{cr} value on Day -1 (calculated by Cockcroft-Gault equation) will be calculated and recorded.

In order to safeguard subject safety, this study will enroll subjects with renal impairment in a staggered fashion. A single oral dose of 100 mg lorlatinib will be administered first to subjects with mild renal impairment (Group B). After single 100 mg oral dose of lorlatinib is tolerated in at least 3 subjects with mild renal impairment, subjects with moderate renal impairment (Group C) will be enrolled one at a time and administered a single oral dose of lorlatinib. There will be an observation period of at least 1 week after dosing of the first 3 subjects to evaluate safety and tolerability. Based on the safety and tolerability of the first 3 subjects in Group B, a dose lower than 100 mg of lorlatinib may be considered for Group C, as determined by the Sponsor. After dosing of 3 moderate renal impairment subjects, the PK, safety, and tolerability will be evaluated during an observation period of at least 1 week to confirm whether the selected dose is appropriate. If yes, the remaining subjects in Group C and the subjects in severe group (Group D) will be enrolled and dosed at the same dose. If not, a new, lower dose will be proposed for the remaining subjects in Group C and all subjects in Group D based on available information.

Subjects with normal renal function (Group A) will be matched to the subjects with renal impairment (Groups B, C, and D) and will receive a single oral lorlatinib dose corresponding to the dose level(s) administered in this study with respect to demographically pooled average age (±10 years), weight (±20 kg), and gender (ratio 1:1, ±2 patients per gender). Therefore, enrollment of Group A will begin after all subjects from Groups B, C, and D have completed the PK collection. If a reduced lorlatinib dose is necessary for any renal impaired group(s), an additional control group will be added to match the reduced dose using the same match criteria of average age, weight, and gender.

Plasma samples for the determination of lorlatinib and potential metabolite(s) concentrations and urine samples for the determination of lorlatinib concentrations will be collected up to 120 hours after lorlatinib dose. Therefore, subjects would be expected to be on study for at least 6 days after receiving the lorlatinib dose. Since lorlatinib is not highly protein bound (fraction unbound, f_u = 34%),[7] unbound concentrations of lorlatinib will not be measured in this study.

Subjects will be admitted to the study unit on Day -1 (1 day before dosing) and will be administered a single oral dose of lorlatinib on Day 1. Subjects will be confined to the Clinical Research Unit (CRU) for PK sample collection and AE monitoring until Day 6, through the last PK sample collection. A subject will be considered evaluable at the discretion of the Sponsor Clinical Pharmacologist. Additional subjects may be enrolled to obtain 8 evaluable subjects per group (for Groups A, B, and C) to complete the study. Eight (8) subjects with severe renal impairment (Group D) are expected to be enrolled, but at least 4 subjects in this group should be evaluable (as determined by Sponsor Clinical Pharmacologist) to complete the study.

Physical examinations, triplicate 12-lead ECG, vital sign measurements, and clinical laboratory tests will be conducted and adverse events will be monitored throughout the study to assess safety.

4. SUBJECT ELIGIBILITY CRITERIA

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

In case of screen failure, a subject may be re-screened once after a 30 day period, if the initial screen failure is not due to an Inclusion/Exclusion criterion that results in permanent disqualification from enrollment (eg, medical history). This will be done in consultation with the Sponsor.

4.1. Inclusion Criteria

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

4.1.1. All Subjects

1. Healthy (with the exception of defined renal impairment as described above in Section 3) female subjects of non-childbearing potential and/or male subjects who, at the time of screening, are between the ages of 18 and 75 years, inclusive. Healthy is defined as no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure (BP) and pulse rate measurement, 12-lead ECG, or clinical laboratory tests.

   Female subjects of non-childbearing potential must meet at least 1 of the following criteria:

   a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state;

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

c. Have medically confirmed ovarian failure.

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

2. Body mass index (BMI) of 17.5 to 36 kg/m^2; and a total body weight >50 kg (110 lb).

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

4. Subjects who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.1.2. Subjects with Normal Renal Function (Group A)

1. Normal renal function (eGFR ≥90 mL/min) during the 2-week screening period, based on the average of 2 eGFR values (calculated by the MDRD equation) using 2 SCr values obtained at least 3 days but not more than 14 days apart, as specified in the SCHEDULE OF ACTIVITIES. The 2 eGFR values will need to be within 25% of each other, calculated as (first eGFR– second eGFR)/first eGFR. The eGFR collected within 24 hours of lorlatinib dosing will be used for final subject stratification, group assignment, and PK analysis.

2. Group A subjects will be matched to subjects with renal impairment (Groups B, C, and D) with respect to age, weight and gender.

4.1.3. Subjects with Renal Impairment (Groups B, C, and D)

1. Good general health commensurate with the population with chronic kidney disease.

2. Stable drug regimen, defined as not starting a new drug or changing dosage of currently used medications within seven days or 5 half-lives (whichever is longer) before lorlatinib dosing.

3. Study enrollment and initial renal function stratification is based on the average of 2 eGFR values (calculated by the MDRD equation) using 2 SCr obtained at least 3 days but not more than 14 days apart during the 2-week screening period, as defined in the SCHEDULE OF ACTIVITIES and in Section 3 for mild, moderate, and severe renal impairment. Subjects should demonstrate stable renal function where the 2 eGFR values will need to be within 25% of each other, calculated as (second eGFR – first eGFR)/first eGFR. If the second eGFR value falls outside of 25% of the first eGFR value, a third eGFR may be obtained after at least 3 days and within 14 days of the second eGFR. This third eGFR value will need to be within 25% of the second eGFR value to demonstrate stable renal function, calculated as (third eGFR – second eGFR)/second eGFR. The eGFR collected within 24 hours of lorlatinib dosing will be used for final subject stratification, group assignment, and PK analysis.

4.2. Exclusion Criteria

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

4.2.1. All Subjects

1. Renal allograft recipients.

2. Any condition possibly affecting drug absorption (eg, gastrectomy).

3. A positive urine drug test.

4. History of regular alcohol consumption exceeding 7 drinks/week for female subjects or 14 drinks/week for male subjects (1 drink = 5 ounces [150 mL] of wine or 12 ounces [360 mL] of beer or 1.5 ounces [45 mL] of hard liquor) within 6 months before screening.

5. Treatment with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of investigational product (whichever is longer).

6. Screening supine triplicate 12-lead ECG demonstrating a corrected QT (QTc) interval >450 msec or a QRS interval >120 msec, except for subjects with severe renal impairment (Group D). For subjects with severe renal impairment (Group D), the threshold is screening supine triplicate 12-lead ECG demonstrating a QTc interval >470 msec or a QRS interval >120 msec.

7. Second-degree or third-degree AV block (unless paced) or baseline PR interval >180 msec at any time prior to dosing of study treatment.

8. Subjects with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

   - AST **or** ALT level ≥1.5 × upper limit of normal (ULN);

   - Total bilirubin level ≥1 × ULN; subjects with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

9. Pregnant female subjects; breastfeeding female subjects; fertile male subjects 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 after the last dose of investigational product.

10. History of sensitivity to heparin or heparin-induced thrombocytopenia.

11. History of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C; positive testing for HIV, hepatitis B surface antigen (HepBsAg), hepatitis B core antibody (HepBcAb), or hepatitis C antibody (HCVAb).

12. Unwilling or unable to comply with the criteria in the Lifestyle Requirements section of this protocol.

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

14. 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 investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.2.2. Subjects with Normal Renal Function (Group A)

1. Evidence or history of clinically significant hematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Use of prescription or nonprescription drugs and dietary supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of investigational product. As an exception, acetaminophen/paracetamol may be used at doses of ≤1 g/day. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor.

4.2.3. Subjects with Renal Impairment (Groups B, C, and D)

1. Evidence or history of clinically significant disease that may affect the safety of the subject or that may affect the pharmacokinetics of lorlatinib. A history of diabetes mellitus, hypertension and/or ischemic heart disease are not cause for exclusion as long as the subject is medically stable and any drugs that are administered for these conditions are not expected to interfere with the pharmacokinetics of lorlatinib.

2. Subjects with any significant hepatic, cardiac or pulmonary disease (apart from stable ischemic heart disease), or subjects who are clinically nephrotic.

3. Subjects requiring dialysis.

4. Use of food, drugs, or dietary supplements that may affect the PK of lorlatinib within 7 days or 5 half-lives (whichever is longer) prior to the first dose of lorlatinib. Use of medications that are not believed to affect subject safety and are medically necessary for the treatment and maintenance of renal disease and other pre-existing and/or concurrent stable comorbid conditions are only permitted following approval by the Sponsor. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the Sponsor.

5. 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 inhibitors (eg, boceprevir, cobicistat, clarithromycin, conivaptan, diltiazem, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, tipranavir, troleandomycin, voriconazole, grapefruit juice or grapefruit/grapefruit-related citrus fruits [eg, Seville oranges, pomelos]). The topical use of these medications (if applicable), such as 2% ketoconazole cream, is allowed.

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

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

6. Concurrent use of CYP3A substrates with narrow therapeutic indices (eg, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl including transdermal patch, pimozide, quinidine, sirolimus, tacrolimus) within 12 days prior to the first dose of lorlatinib.

4.3. Lifestyle Requirements

The following guidelines are provided:

4.3.1. Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations and 10 hours prior to the collection of the pre-dose PK sample. Water is permitted until 1 hour prior to investigational product administration.

- On Day 1, subjects will continue to fast for 4 hours after lorlatinib dosing, except for diabetics who may have a snack 2 hours after dosing, if required.

- On Day 1, water may be consumed without restriction beginning 1 hour after lorlatinib dosing. Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices-see below) may be consumed with meals and the evening snack.

- On Day 1, lunch will be provided approximately 4 hours after lorlatinib dosing.
- On Day 1, dinner will be provided approximately 9 to 10 hours after lorlatinib dosing.
- An evening snack may be permitted.
- Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (eg, Seville oranges, pomelos) from 7 days prior to the first dose of investigational product until collection of the final PK blood sample.
- While confined, the total daily nutritional composition will be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per subject will not exceed approximately 3200 kcal.

4.3.2. Alcohol, Caffeine, and Tobacco

- Subjects will abstain from alcohol for 24 hours prior to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample. Subjects may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator at any time during the study.
- Subjects will abstain from caffeine-containing products for 24 hours prior to the start of lorlatinib dosing until collection of the final PK sample.
- Subjects will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to lorlatinib dosing and during confinement in the CRU.

4.3.3. Activity

- Subjects will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, and aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

4.3.4. Contraception

All malesubjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for 97 after the last dose of investigational product. The investigator or his/her designee, in consultation with the subject, will confirm the subject has selected the most appropriate method of contraception for the individual subject and his female partner from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use. Subjects need to affirm that they meet at least one of the selected methods of contraception. The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the SCHEDULE OF ACTIVITIES and document such conversation in the subject's chart. In addition, the investigator or his/her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, or implanted hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

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

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

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

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

NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including 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.

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

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 (roster) located in the team SharePoint site.

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

advice on medical questions or problems that may arise during the study. For sites other than a Pfizer CRU, the contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

5. STUDY TREATMENTS

For the purposes of this study, and per International Council 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 is lorlatinib.

5.1. Allocation to Treatment

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

5.2. Subject Compliance

Investigational product will be administered under the supervision of investigator site personnel. The oral cavity of each subject will be examined following dosing of lorlatinib tablets to ensure the investigational product was taken.

5.3. Investigational Product Supplies

5.3.1. Dosage Form and Packaging

Lorlatinib 25 mg CCI tablets will be supplied by Pfizer to the CRU in bulk along with individual dosing containers and desiccants for individual oral subject dosing as needed. Lorlatinib 25 mg tablets will be presented to the subjects in an individual dosing container.

Lorlatinib 25 mg tablets will be supplied to the CRU as packaged bulk bottles and labeled according to local regulatory requirements. The bottles will be provided to the site for dispensing by the pharmacy.

5.3.2. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the investigational product ready for administration or dispensing to the subject/caregiver by qualified staff. Dispensing is defined as the provision of investigational product, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, subject, or caregiver in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

The 100 mg dose consisting of four 25 mg oral tablets of lorlatinib will be prepared at the CRU in the individual dosing containers by 2 operators, one of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist). The tablets will be provided in individual subject bottles along with appropriate desiccant canister(s), and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

5.4. Administration

Following an overnight fast of at least 10 hours, subjects will receive a 100 mg dose (or an appropriately selected dose based on subject PK, safety, and tolerability) of lorlatinib tablets with approximately 240 mL of ambient temperature water at approximately 0800 hours (plus or minus 3 hours).

Subjects will swallow the lorlatinib tablets whole, and will not manipulate or chew the medication prior to swallowing.

In order to standardize the conditions on PK sampling days, all subjects will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing of lorlatinib.

5.5. Investigational Product Storage

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

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

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

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

5.6. Investigational Product Accountability

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

5.6.1. Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

Subjects will abstain from concomitant treatments as described in Section 4.2, except for the treatment of AEs. Limited use of nonprescription medications that are not believed to affect subject safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. For subjects with renal impairment (Groups B, C, and D), any drugs that are administered for renal disease or other pre-existing conditions as specified in Section 4.2 are permitted, following approval of the Sponsor, as long as the subject is medically stable and use of the drugs are not expected to interfere with the pharmacokinetics of lorlatinib.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of investigational product will be documented as a prior treatment. Treatments taken after the first dose of investigational product will be documented as concomitant treatments.

6. STUDY PROCEDURES

6.1. Screening

Subjects will be screened within 14 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study. The investigator (or an appropriate delegate at the investigator site) will obtain informed consent from each subject in accordance with the procedures described in the Subject Information and Consent section. If the time between Screening and dosing exceeds 14 days as a result of unexpected delays (eg, delayed drug shipment), then subjects do not require rescreening if the Day -1 laboratory results meet the eligibility criteria.

A subject who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided the Day -1 laboratory results meet the eligibility criteria for this study. CCI [redacted]

The following procedures will be completed:

- Obtain written informed consent.
- Confirm and document that the subject meets the inclusion/exclusion criteria.
- The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the contraception guidelines and will confirm highly-effective, proper contraception is being used.
- Collect demography (subject race, ethnicity, date of birth, age, gender).
- Collect height and weight.
- Obtain medical history, including history of prior illegal drug, alcohol, and tobacco use.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 28 days prior to the planned first dose.
- Obtain single supine BP and pulse rate pulse rate after at least 5 minutes of rest in a supine position.
- Conduct full physical examination (PE) (to be performed by trained medical personnel at the investigator site). The screening physical examination may be performed on Day -1.
- Collect triplicate 12-lead ECG.

- Assess baseline symptoms/AEs.
- Following at least an overnight fast, collect blood and urine specimens for the following:
  - Safety laboratory tests (hematology, clinical chemistry, and urinalysis);
  - Urine drug test (mandatory) and alcohol breath test at discretion of the investigator;
  - Serum FSH concentration for any female subjects who has been amenorrheic for at least 12 consecutive months;
  - Collect blood for HIV, HepBsAg, HepBcAb or HCVAb testing;
  - Serum creatinine and eGFR calculation.

To prepare for study participation, subjects will be instructed on the information in the Section 4.3 and Section 5.7 of the protocol.

6.2. Study Period

For the study period described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

- ECGs: obtain prior to vital sign measurements and as close as possible to the scheduled time, but prior to blood specimen collection;
- BP/pulse rate: obtain as close as possible to the scheduled time, but prior to blood specimen collection;
- PK blood specimens: obtain at the scheduled time;
- Other procedures: obtain all other procedures as close as possible to the scheduled time, but may be obtained before or after blood specimen collection.

When an intravenous (IV) catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate, BP, and oral temperature) should be collected prior to the insertion of the catheter.

6.2.1. Day -1

Subjects will be admitted to the CRU on Day -1 prior to Day 1 dosing. The following procedures will be completed following admission to the CRU:

- Review inclusion and exclusion criteria.

- Obtain blood and urine samples for safety laboratory tests (hematology, clinical chemistry, urinalysis) after overnight fast. The results must have no clinically significant findings, as judged by the Investigator, in order for a subject to be given investigational product on Day 1.

- Obtain weight.

- Collect urine for drug testing (mandatory) and alcohol breath test at discretion of the Investigator. These tests may be performed at any other time at the discretion of the investigator.

- The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the contraception guidelines and will confirm highly effective contraception is being used.

- Serum creatinine, eGFR, and creatinine clearance calculation.

- Collect triplicate 12-lead ECG.

- Obtain single supine BP and pulse rate pulse rate after at least 5 minutes of rest in a supine position.

- Collect CCI [redacted] a blood sample for pharmacogenomics on Day -1. CCI [redacted]

- Assess baseline symptoms/AEs.

- Review prior and concomitant medication(s).

- Review changes in the subject's medical history, including medication history since Screening.

- Conduct full PE, if deferred from the Screening visit. A limited PE may be performed at other designated time points at the discretion of the investigator.

6.2.2. Day 1

Prior to lorlatinib dosing, the following procedures will be completed:

- Assess baseline symptoms/AEs.

- Collect triplicate 12-lead ECG measurements prior to insertion of the IV catheter.

- Collect supine BP and pulse rate prior to insertion of the IV catheter.

- Collect blood samples for PK analysis of lorlatinib and its metabolite(s).
- Collect a blank urine sample of at least 50 mL for all subjects. Each subject will empty his or her bladder just prior to dosing.
- After all pre-dose procedures have been completed, administer the investigational product (see Section 5.4).

After dosing, the following procedures will be completed:

- Subject should be supine for at least 10 minutes prior to triplicate 12-lead ECG measurements at 1, 2, 4 hours after dosing.
- Assess supine BP and pulse rate at 1, 2, and 4 hours after dosing.
- Collect blood samples for PK analysis at 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours following dosing on Day 1.
- Collect urine during the interval of 0 to 24 hours after dosing on Day 1.
- Review concomitant treatments.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”

6.2.3. Day 2

The following procedures will be completed:

- Assess supine BP and pulse rate 24 hours after dosing on Day 1.
- Obtain triplicate 12-lead ECG measurements 24 hours after dosing on Day 1.
- Collect fasting blood and urine samples for safety laboratory tests (hematology, clinical chemistry, urinalysis) 24 hours after dosing on Day 1.
- Collect blood samples for PK analysis of lorlatinib and its metabolite(s) at 24 hours after dosing on Day 1.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as “How do you feel?”
- Review concomitant treatments.
- Collect urine during the interval of 24 to 48 hours after dosing on Day 1.

6.2.4. Day 3

The following procedures will be completed:

- Collect blood samples for PK analysis 48 hours after dosing on Day 1.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "How do you feel?"
- Collect urine during the interval of 48 to 72 hours after dosing on Day 1.
- Review concomitant treatments.

6.2.5. Day 4

The following procedures will be completed:

- Collect blood samples for PK analysis 72 hours after dosing on Day 1.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "How do you feel?"
- Collect urine during the interval of 72 to 96 hours after dosing on Day 1.
- Review concomitant treatments.

6.2.6. Day 5

The following procedures will be completed:

- Collect blood samples for PK analysis 96 hours after dosing on Day 1.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "How do you feel?"
- Collect urine during the interval of 96 to 120 hours after dosing on Day 1.
- Review concomitant treatments.

6.2.7. Day 6

Subjects may be discharged from the CRU after the completion of assessments. The following procedures will be completed 120 hours after lorlatinib dosing on Day 1:

- A limited PE will be conducted.
- Collect fasting blood and urine sample for safety laboratory tests (hematology, clinical chemistry, urinalysis).

- The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the contraception guidelines and will confirm highly-effective, proper contraception is being used.

- Subject should be supine for at least 10 minutes prior to triplicate 12-lead ECG measurements.

- Assess supine BP and pulse rate.

- Collect blood samples for PK analysis 120 hours after dosing on Day 1.

- Collect urine during the interval of 120 hours after dosing on Day 1.

- Review concomitant treatments.

- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a nonleading question such as "How do you feel?"

- Discharge from CRU confinement.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the Pfizer medical monitor (or designated representative) should be notified and the subject may be asked to remain in the CRU until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain in the CRU and/or when outpatient follow-up is deemed appropriate, the Pfizer medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3. Follow-up

6.3.1. Follow-up Visit

Subjects will return to the CRU for follow-up visit at the discretion of the principal investigator (PI) or if the subject withdraws consent or if there are unresolved AE at discharge. At this visit, the following procedures may include, but are not limited to:

- Conduct limited PE and weight measurement.

- The investigator or his/her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the contraception guidelines and will confirm highly-effective, proper contraception is being used.

- Assess supine BP and pulse rate.

- Obtain information regarding the use of concomitant treatment and the occurrence of AEs.

- Review concomitant treatments.

6.4. Follow-up Contact

Follow-up contact will be completed at least 28 calendar days after the last administration of the investigational product to capture any potential adverse events (see Section 8.1.4) and to confirm appropriate contraception usage (see Section 4.3.4). Contact with the subject may be done via a phone call.

6.5. Subject Withdrawal /Early Termination

Withdrawal of consent:

Subjects 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 subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects 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 investigational product or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate case report form (CRF) page. In the event that vital status (whether the subject 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 subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. All attempts should be documented in the subject's medical records. If it is determined that the subject 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 subject's informed consent, then the investigator may use a sponsor-retained third-party representative to assist site staff with obtaining the subject'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 subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see Section 8.1.3) or behavioral reasons, or the inability of the subject to comply with the

protocol-required schedule of study visits or procedures at a given investigator site. The early termination visit applies only to subjects who are randomized and then are prematurely withdrawn from the study.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The investigator or site staff should attempt to contact the subject twice. After 2 attempts, CRU staff may send a registered letter. If no response is received from the subject, the subject will be considered lost to follow-up. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

It may be appropriate for the subject to return to the clinic for final safety assessments to be scheduled as early as practically feasible following the decision to withdraw from the study. Subjects should be questioned regarding their reason for withdrawal. At the early-withdrawal visit, every effort must be made to complete the following assessments:

- Limited PE, if there is a new or open AE or clinically significant abnormal physical finding from the last visit;
- Supine BP and pulse rate measurements;
- Triplicate 12-lead ECG measurement;
- Blood and urine specimens for safety laboratory;
- Blood sample for PK analysis.

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

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

Subjects who withdraw from the study may be replaced at the discretion of the investigator upon consultation with the sponsor.

7. ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive

actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

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

7.1. Safety

7.1.1. Laboratory Tests

The following safety laboratory tests will be performed at times defined in the STUDY PROCEDURES section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety concerns.

Table 5. Safety Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea and creatinine	pH	FSH[b]
Hematocrit	Glucose (fasting)	Glucose (qual)	Urine drug screening
RBC count	Calcium	Protein (qual)	Hepatitis B surface
MCV	Sodium	Blood (qual)	antigen[c]
MCH	Potassium	Ketones	Hepatitis B core
MCHC	Chloride	Nitrites	antibody[c]
Platelet count	Total CO_2 (bicarbonate)	Leukocyte esterase	Hepatitis C core
WBC count	AST, ALT	Urobilinogen	antibody[c]
Total neutrophils (Abs)	Total bilirubin	Urine bilirubin	HIV[c]
Eosinophils (Abs)	Alkaline phosphatase	Microscopy[a]	
Monocytes (Abs)	Uric acid		
Basophils (Abs)	Albumin		
Lymphocytes (Abs)	Total protein		
	Lipase		
	Amylase		
	Additional Tests (Needed for Hy's Law):		
	AST, ALT (repeat)		
	Total bilirubin (repeat)		
	Albumin (repeat)		
	Alkaline phosphatase (repeat)		
	Direct bilirubin		
	Indirect bilirubin		
	Creatine kinase		
	GGT		
	PT/INR		

a Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.
b At Screening only, in females who are amenorrheic for at least 12 consecutive months.
c At Screening only.

- The minimum requirement for drug screening includes cocaine, tetrahydrocannabinol (THC), opiates/opioids, benzodiazepines, and amphetamines.

- Subjects may undergo random urine drug testing at the discretion of the Investigator. Drug testing conducted prior to dosing must be negative for subjects to receive investigational product.

7.1.2. Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems. The limited or abbreviated physical examination will be focused on general appearance, the respiratory and cardiovascular systems, and subject-reported symptoms.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

7.1.3. Blood Pressure and Pulse Rate

BP and pulse rate will be measured at times specified in the SCHEDULE OF ACTIVITIES section of this protocol. Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

Supine BP will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Subjects should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

7.1.4. Electrocardiogram

Triplicate 12-Lead ECGs should be collected at times specified in the SCHEDULE OF ACTIVITIES section of this protocol.

All scheduled ECGs should be performed after the subject has rested quietly for at least 10 minutes in a supine position.

Triplicate 12-lead ECGs will be obtained approximately 2 to 4 minutes apart; the average of the triplicate ECG measurements collected at pre-dose of Day 1 will serve as each subject's time-controlled baseline QTc value.

If the average of QTc values from the triplicate measurements remains above the threshold value (ie, is ≥45 msec from the baseline, or is ≥500 msec), then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If QTc values remain ≥500 msec (or ≥45 msec from the baseline) for greater than 4 hours (or sooner, at the discretion of the investigator), or QTc intervals get progressively longer, the subject should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than 500 msec (or to <45 msec above the baseline) after 8 hours of monitoring (or sooner, at the discretion of the investigator).

If subject develops new first degree block as defined by PR interval greater than 280 msec, if patient is found to have a second degree or higher AV block, or if patient has symptomatic bradycardia, patient should undergo continuous cardiac monitoring with 12-lead ECG taken every hour until PR interval returns to <220 msec, until AV block resolves or until symptoms resolve. If patient develops high degree AV block defined as second degree AV block, Mobitz II or third degree block, patient should be referred to a cardiologist for further evaluation.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads are placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

7.2. Pharmacokinetics

7.2.1. Plasma for Analysis of Lorlatinib and Its Metabolite(s)

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

In addition to samples collected at the scheduled times, an additional blood sample should 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.

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

At each designated time, blood samples (8.0 mL) to provide approximately 3.5 mL plasma (aliquoted into 3 × 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 dipotassium ethylenediaminetetraacetic acid (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.

- Samples will be analyzed for lorlatinib and metabolite(s) using a validated analytical method in compliance with Pfizer standard operating procedures (SOPs).

- 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.

- As part of understanding the PK of the investigational product, samples may be used for metabolite identification and/or evaluation of the bioanalytical method, CCI [redacted] These data will not be included in the CSR.

7.2.2. Urine for Analysis of Lorlatinib

Urine will be collected at times specified in the SCHEDULE OF ACTIVITIES section of the protocol. Each subject will empty his or her bladder just prior to dosing.

Samples will be analyzed using a validated analytical method in compliance with Pfizer SOPs.

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.

CCI [redacted]

7.3. Pharmacogenomics

7.3.1. Genotyping Analysis (If Applicable; Pertains but is not Limited to Blood, Buccal Swabs, Saliva, and/or Tissue)

Blood samples for genotyping will be examined to assess the impact of allelic variants of drug-metabolizing enzymes and transporters. Additionally, these samples may also be used for retrospective evaluation of additional genetic variants associated with variation in PK or to explore AEs should these be observed. Samples will be retained for a period of up to 3 years after regulatory approval.

A 4-mL blood sample will be collected from each subject into a plastic K_2EDTA tube at times specified in the SCHEDULE OF ACTIVITIES section of the protocol.

Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures

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

CCI [redacted]

CCI

[redacted]

7.5. Blood Volume

The total blood sampling volume for individual subjects in this study is approximately 158 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

7.6. Potential Cases of Acute Kidney Injury

Abnormal values in serum creatinine concurrent with presence or absence of increase in blood urea nitrogen (BUN) that meet the criteria below, in the absence of other causes of kidney injury, are considered potential cases of acute kidney injury and should be considered important medical events.

An increase of ≥0.3 mg/dL (or ≥26.5 μmol/L) in SCr level relative to the subject's own baseline measurement should trigger another assessment of SCr as soon as practically feasible, preferably within 48 hours from awareness.

If the second assessment (after the first observations of ≥0.3 mg/dL (or ≥26.5 μmol/L) in SCr relative to the subject's own baseline measurement) is ≥0.4 mg/dL (or ≥35.4 μmol/L), the subject should be discontinued from the study and adequate, immediate, supportive measures taken to correct apparent acute kidney injury.

Subjects should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the second assessment confirming abnormal SCr result. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating SCr, laboratory tests should include serum BUN, serum creatinine kinase, and serum electrolytes (including at a minimum potassium, sodium, phosphate/phosphorus, and calcium), in addition to urinary dipstick, urine microscopic examination, and urinary indices. All cases confirmed on repeat testing as meeting the laboratory criteria for acute kidney injury, with no other cause(s) of laboratory abnormalities identified, should be considered potential cases of drug-induced kidney injury irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal SCr. If ≥2 healthy subjects in any renal function group are noted to have 2 *consecutive* SCr results of ≥0.3 mg/dL (or ≥26.5 μmol/L), an assessment of whether the finding may be considered an adverse drug reaction should be undertaken.

8. ADVERSE EVENT REPORTING

8.1. Requirements

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

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Non-serious AE	All	None
Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

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

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

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

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

investigator to provide clarity and understanding of the event in the context of the clinical study.

8.1.1. Additional Details on Recording Adverse Events on the CRF

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

8.1.2. Eliciting Adverse Event Information

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

8.1.3. Withdrawal From the Study Due to Adverse Events (see also the Subject Withdrawal /Early Termination Section)

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

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

8.1.4. Time Period for Collecting AE/SAE Information

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including the follow-up visit. At least 28 calendar days after the lorlatinib dose, the subject will be contacted by telephone to inquire about SAEs, including hospitalizations and newly diagnosed chronic medical conditions since the last visit.

8.1.4.1. Reporting SAEs to Pfizer Safety

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

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

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

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.

8.1.5. Causality Assessment

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

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

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

8.2. Definitions

8.2.1. Adverse Events

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

- Abnormal test findings;
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- 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.

8.2.2. Abnormal Test Findings

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

- Test result is associated with accompanying symptoms; and/or

- Test result requires additional diagnostic testing or medical/surgical intervention; and/or

- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or

- Test result is considered to be an AE by the investigator or sponsor.

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

8.2.3. Serious Adverse Events

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

- Results in death;

- Is life-threatening (immediate risk of death);

- Requires inpatient hospitalization or prolongation of existing hospitalization;

- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

- Results in congenital anomaly/birth defect.

  Or that is considered to be:

  - An important medical event.

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

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

8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a

tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

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

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

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

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

If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed 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 subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

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

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

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

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

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

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

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

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 Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.4.2.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

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

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

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless

pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

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

8.4.2.2. 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 subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.4.3. Medication Errors

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

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

8.4.3.1. Medication Errors

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

Medication errors include:

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

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

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

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

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

9. DATA ANALYSIS/STATISTICAL METHODS

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

9.1. Sample Size Determination

Approximately, 8 subjects will be enrolled into each of the normal, mild, moderate, and severe renal impairment groups as described in Section 3.1. The sample size is based on recommendations from the "Food and Drug Administration (FDA) Guidance for Industry - Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling".

Subjects who discontinue from the study before completing all assessments may be replaced at the discretion of the investigator and Sponsor to ensure 8 evaluable subjects in each of normal, mild, and moderate impairment groups (Groups A, B, and C) and at least 4 evaluable subjects in severe group (Group D).

9.2. Pharmacokinetic Analysis

The PK concentration population is defined as all subjects enrolled and treated and who have at least 1 lorlatinib concentration.

The PK parameter analysis population is defined as all subjects enrolled and treated who have at least 1 of the PK parameters of primary interest.

Subjects are considered PK evaluable if all PK concentrations are available or at the discretion of the Sponsor Clinical Pharmacologist.

9.2.1. Derivation of Pharmacokinetic Parameters Prior to Analysis

Pharmacokinetic parameters following single dose administration will be derived from the concentration-time profile as follows:

Table 6. Derivation of Pharmacokinetic Parameters

Parameters	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration time curve from time 0 to the time of the last quantifiable concentration	Linear-log trapezoidal method.
AUC_{inf}	Area under the plasma concentration-time curve from time 0 extrapolated to time infinity	$AUC_{inf} = AUC_{last} + (C_{last}/k_{el})$ C_{last}, plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis. k_{el}, terminal elimination phase rate constant estimated by linear regression based on the observations justified to describe the terminal phase on log-linear concentration-time profile.
C_{max}	peak or maximum observed plasma concentration	Observed directly from data
T_{max}	Time to C_{max}	Observed directly from data as time of first occurrence
$t_{½}$	Terminal plasma elimination half-life	$Ln(2)/k_{el}$
CL/F	Apparent clearance after oral dose	$Dose/AUC_{inf}$ after oral dose
V_z/F	apparent oral volume of distribution	$Dose/(AUC_{inf} \times k_{el})$ after oral dose
CL_R	Renal clearance	Ae/AUC_{last}

Table 6. Derivation of Pharmacokinetic Parameters

Parameters	Definition	Method of Determination
Ae	Cumulative amount of drug recovered unchanged in the urine, from zero to time 120 hours post-dose	Sum of [urine concentration × sample volume[a]] for each collection interval.
Ae%	Cumulative amount of drug recovered unchanged in the urine, from zero to time 120 hours post-dose, expressed as fraction of administered dose	Ae/Dose*100%
MRC_{max}	Metabolite(s) to parent ratio for C_{max}	$(C_{max}/MW)_{metabolite}/(C_{max}/MW)_{parent}$
$MRAUC_{last}$	metabolite(s) to parent ratio for AUC_{last}	$(AUC_{last}/MW)_{metabolite}/AUC_{last}/MW)_{parent}$
$MRAUC_{inf}$	metabolite(s) to parent ratio for AUC_{inf}	$(AUC_{inf}/MW)_{metabolite}/AUC_{inf}/MW)_{parent}$

MW: Molecular Weight
[a] Sample volume = (urine weight in g/1.020), where 1.020 g/mL is the approximate specific gravity of urine.

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

9.2.2. Statistical Methods

Analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{inf} (if data permit), AUC_{last} and C_{max} between the normal renal function group and each of the renal impairment groups. Point estimates and associated 90% confidence intervals (CIs) for the difference of each comparison will be estimated and exponentiated to provide geometric mean ratios and associated 90% CIs.

Regression analysis will be conducted to characterize the relationship between renal function and PK parameter CL/F. Both CL_{cr} calculated from the C-G formula and eGFR obtained from the MDRD equation on Day -1 will be used in regression analysis. Analysis results will include estimates of parameters for the chosen model as well as measures of precision such as CI or standard errors.

PK parameters AUC_{inf}, C_{max}, AUC_{last}, time for C_{max} (T_{max}), terminal plasma elimination half-life ($t_{½}$), CL/F, CL_R, V_z/F, cumulative amount of drug recovered unchanged in the urine, from zero to time 120 hours post-dose (Ae), cumulative amount of drug recovered unchanged in the urine, from zero to time 120 hours post-dose, expressed as fraction of administered dose (Ae%), will be summarized descriptively by analyte (eg, lorlatinib and its metabolite(s)) and renal function group. Metabolite(s) to parent ratio for C_{max} (MRC_{max}), metabolite(s) to parent ratio for AUC_{last} ($MRAUC_{last}$), and metabolite(s) to parent ratio for AUC_{inf} ($MRAUC_{inf}$) will also be summarized descriptively by renal function group.

For AUC_{inf}, AUC_{last} and $C_{max,}$ box-whisker plots of the parameters will be plotted by analyte and renal function group. Individual concentrations will be listed and summarized descriptively by group and PK sampling time. Individual subject and summary profiles (means and medians) of the concentration-time data will be plotted across different groups.

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

9.3. Analysis of Other Endpoints

Pharmacogenomic and biomarker data will be collected and retained for future analyses, but may not be analyzed, specifically, for this study.

9.4. Safety Analysis

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of subjects. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4.1. Electrocardiogram Analysis

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS interval will be summarized by treatment and time.

The number (%) of subjects with maximum post-dose QTc values and maximum increases from baseline in the following categories will be tabulated by treatment:

Table 7. Safety QTc Assessment

	Borderline (msec)	Prolonged (msec)
Absolute value	--	≥480
Absolute change	30-<60	≥60

In addition, the number of subjects with corrected and uncorrected QT values ≥500 msec will be summarized.

The number (%) of subjects with maximum post-dose PR interval values, maximum increases from baseline and second degree atrioventricular block (AVB) type 2 or higher in the following categories will be tabulated by renal function group (Table 8):

Table 8. Safety PR Interval

	msec
Absolute Value	≥200 - <220
	≥220 - <240
	≥240 - <260
	≥260
Absolute Change	40-<60
	60-<80
	≥80
Relative Change from baseline	>25%
Second-degree AVB type 2 or higher[a]	

a. Second degree block type 2 or higher would be determined by the ECG machine and confirmed by a physician.

9.5. Interim Analysis

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

9.6. Data Monitoring Committee

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

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

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

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's medical records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

For studies conducted at non-Pfizer investigator sites, 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/Data Collection Tools/Electronic Data Record

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

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

The investigator 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 those charts.

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

11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or 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 subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

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

12.3. Subject Information and Consent

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

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

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

The investigator must ensure that each study subject, is fully informed about the nature and objectives of the study and possible risks associated with participation.

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

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

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

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in the United States

Last subject last visit (LSLV) is defined as the date the investigator reviews the last subject's final safety data and determines that no further evaluation is required for the subject to complete the trial.

14. SPONSOR DISCONTINUATION CRITERIA

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

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. 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 study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

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

www.clinicaltrials.gov

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

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

EudraCT

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

www.pfizer.com

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

15.2. Publications by Investigators

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

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

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

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

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

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

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

16. REFERENCES

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4. Bergethon K*, et al.* (2012) ROS1 Rearrangements Define a Unique Molecular Class of Lung Cancers. *Journal of Clinical Oncology* 30(8):863-870.

5. JANSSEN_Pharmaceuticals (2014) SPORANOX- itraconazole solution label.

6. SmPC Sporanox®, Belgium.

7. PF-06463922 Investigator's Brochure 2016.

Appendix 1. Abbreviations

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

Abbreviation	Term
Abs	Absolute
ADME	absorption, distribution, metabolism, excretion
Ae	cumulative amount of drug recovered unchanged in the urine, from zero to time 120 hours post-dose
Ae%	cumulative amount of drug recovered unchanged in the urine, from zero to time 120 hours post-dose, expressed as fraction of administered dose
AE	adverse event
ALK	Anaplastic Lymphoma Kinase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
AUC_{inf}	area under the plasma concentration-time curve from time 0 extrapolated to time infinity
AUC_{last}	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AV	Atrioventricular
AVB	atrioventricular block
BA	Bioavailability
CCI	[redacted]
BID	twice a day
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
Cb/Cp	blood to plasma concentration ratios
C_{eff}	efficacious concentration
CHO	Chinese Hamster Ovary
CI	confidence interval
CK	creatine kinase
CL	Clearance
CL_{cr}	creatinine clearance
CL/F	apparent clearance after oral dose
CL_r	renal clearance
C_{max}	peak or maximum observed concentration

Abbreviation	Term
CNS	central nervous system
CO_2	carbon dioxide (bicarbonate)
CRF	case report form
CRM	continual reassessment method
CRU	clinical research unit
CSA	clinical study agreement
CSF	cerebrospinal fluid
CSR	clinical study report
CT	clinical trial
CTC	Common Terminology Criteria
%CV	coefficient of variation
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug-interaction
DILI	drug-induced liver injury
DLT	dose limiting toxicities
DMC	data monitoring committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	Electrocardiogram
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EML4	echinoderm microtubule-associated protein-like 4
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
FOB	functional observation battery
FSH	follicle-stimulating hormone
f_u	fraction unbound
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
HCVAb	hepatitis C antibody
HepBcAb	hepatitis B core antibody
HepBsAg	hepatitis B surface antigen
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HLM	human liver microsomes
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICH	International Council on Harmonisation

Abbreviation	Term
ID	Identification
IND	investigational new drug application
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IV	Intravenous
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LOAEL	lowest observed adverse effect level
LFT	liver function test
LSLV	last subject last visit
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDCK-MDR1	Madin Darby canine kidney with multidrug resistance protein 1
MDRD	Modification of Diet in Renal Disease
$MRAUC_{inf}$	metabolite(s) to parent ratio for AUC_{inf}
$MRAUC_{last}$	metabolite(s) to parent ratio for AUC_{last}
MRC_{max}	metabolite(s) to parent ratio for C_{max}
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MW	molecular weight
N/A	not applicable
NADPH	nicotinamide adenine dinucleotide phosphate
NOEL	no observed effect level
NSCLC	non-small-cell lung carcinoma
PCD	primary completion date
PD	pharmacodynamic(s)
PE	physical examination
P-gp	P-glycoprotein
PGx	pharmacogenomic(s)
pH	potential of hydrogen
PI	principal investigator
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PT	prothrombin time
QD	once daily
QTc	corrected QT
qual	Qualitative
R_{ac}	observed accumulation ratio
RBC	red blood cell
ROS1	c-ros oncogene 1
RP2D	recommended Phase 2 dose

Abbreviation	Term
RNA	ribonucleic acid
R_{ss}	steady state accumulation ratios
RTK	receptor tyrosine kinases
SAE	serious adverse event
SAP	statistical analysis plan
S_{Cr}	serum creatinine
$S_{cr,std}$	serum creatinine measured with a standardized assay for serum creatinine
SOP	standard operating procedure
SRSD	single reference safety document
$t_{½}$	terminal plasma elimination half-life
TBili	total bilirubin
THC	Tetrahydrocannabinol
TKI	tyrosine kinase inhibitor
T_{max}	time for C_{max}
ULN	upper limit of normal
US	United States
V_z/F	volume of distribution
WBC	white blood cell