SINGLE-ARM STUDY TO EVALUATE THE SAFETY OF LORLATINIB IN ALK INHIBITOR-TREATED UNRESECTABLE ADVANCED AND/OR RECURRENT ALK-POSITIVE NON-SMALL CELL LUNG CANCER PARTICIPANTS IN INDIA

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Document History

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Original protocol	30 March 2020	Not Applicable (N/A)

ABBREVIATION

Abbreviation	Definition
AE	adverse event
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AV	atrioventricular
bpm	beat per minute
BUN	blood urea nitrogen
CAP	chest abdomen pelvis
CI	confidence interval
CNS	central nervous system
CR	complete response
CRF	case report form
CSA	Clinical Study Agreement
CT	computed tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome
DCIS	ductal carcinoma in situ
DoR	duration of response
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic CRF
ECOG	Eastern Cooperative Oncology Group
EDP	exposure during pregnancy
FDG	fluorodeoxyglucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
hCG	human chorionic gonadotropin
HDL	high-density lipoprotein
HDPE	high-density polyethylene
HRT	hormonal replacement therapy
IC-DoR	intracranial duration of response
IC-ORR	intracranial objective response rate
ICH	International Council for Harmonisation
ILD	interstitial lung disease
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IVRS	interactive voice response system
IWRS	interactive web response system
LDL	low-density lipoprotein
LPFV	last participant last visit
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
N	number of participants
NCI	National Cancer Institute
NTI	narrow therapeutic index
NSCLC	non-small-cell lung cancer

Abbreviation	Definition
ORR	objective response rate
P-gp	permeability glycoprotein
PASS	post-authorization safety study
PD	progressive disease
PET	positron emission tomography
PR	partial response
PS	performance status
PT	prothrombin time
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval calculated using Fridericia's correction factor
PVC	premature ventricular complex
RECIST	Response Evaluation Criteria in Solid Tumor
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SRSD	Single Reference Safety Document
TEAE	treatment-emergent adverse event
TG	triglyceride
TIA	transient ischemic attack
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman of childbearing potential

PROTOCOL SUMMARY

Background

Lung cancers that harbor chromosomal rearrangements of anaplastic lymphoma kinase (ALK) constitute about 3-5% of non-small-cell lung cancers (NSCLCs) and are highly responsive to small-molecule tyrosine kinase inhibitors (TKIs) that target ALK. Standard treatment of patients with advanced ALK-positive NSCLC has recently shifted from sequential crizotinib followed by more potent second-generation ALK TKIs to front-line second-generation TKIs. Whereas most patients derive clinical benefit from second-generation ALK TKIs, acquired resistance invariably develops and leads to clinical relapse.[1]

Lorlatinib is a third-generation, oral, reversible, adenosine triphosphate (ATP)-competitive, macrocyclic TKI of ALK and ROS1. Compared with second-generation inhibitors, lorlatinib was specifically designed to penetrate the central nervous system (CNS) and to overcome known secondary resistance mutations in the ALK tyrosine kinase domain. Preclinical studies demonstrate that lorlatinib is more potent than earlier-generation TKIs against nonmutant ALK and retains potency against most known single ALK resistance mutations, including the highly refractory ALK G1202R solvent front mutation.[2]

In the pivotal single arm, multicenter Phase 2 study, treatment with lorlatinib showed clinically relevant response rates and durable response in patients with ALK-positive NSCLC who had previously received at least 1 ALK TKI, including the second-generation drugs ceritinib and alectinib.[1] In the cohort of patients previously treated with a second-generation ALK TKI (number of patients [N]=28), objective responses were observed in 9 patients (32% [95% confidence interval [CI]: 15.9-52.4]). Substantial intracranial activity was also observed in these patients suffering from frequent brain metastases. The proportion of patients with objective intracranial response to lorlatinib was 55.6% (95% CI: 21.2-86.3) in patients with at least 1 measurable brain lesion at baseline (N=9). The overall and intracranial median duration of response (DoR) were not reached (95% CI: 4.1 months – not reached; duration of follow-up 7 months).

Rationale

On the basis of pivotal Phase 1/2 Study B7461001, lorlatinib received conditional marketing authorization by the Indian Ministry of Health for the treatment of ALK fusion gene-positive unresectable advanced and/or recurrent NSCLC with resistance or intolerance to ALK TKI(s).

In view of the lack of Indian participants from Study B7461001 and of the limited number from the ongoing Phase 3 Study B7461006 (CROWN), the Indian Ministry of Health requested the Sponsor to conduct a post-approval study to obtain additional data on participants in India. The study will be conducted as a post-authorization safety study (PASS).

Study Objectives and Endpoints

Primary Objective

- To evaluate the safety and tolerability of single-agent lorlatinib in participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment.

Secondary Objective

- To evaluate overall and intracranial antitumor activity of single-agent lorlatinib in participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment.

Primary Endpoint

- Incidence of adverse events (AEs).

Secondary Endpoints

- Confirmed objective response rate (ORR), confirmed intracranial objective response rate (IC-ORR), DoR and intracranial duration of response (IC-DoR) as assessed by the Investigator using Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1.

Study Design

This is a Phase 4, open-label, multicenter, non-randomized, prospective, single arm study to evaluate the safety and tolerability of lorlatinib in adult participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment.

This study will enroll enough participants to ensure that 100 participants are treated with lorlatinib.

Study Treatments

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

At the end of study, participants who are on treatment and benefiting from lorlatinib treatment will be moved to commercially available lorlatinib (if considered appropriate by the Investigator) as soon as feasible.

Statistical Methods

The study's objectives are to evaluate the safety, tolerability and antitumor activity of single-agent lorlatinib. This study will enroll enough participants to ensure that 100 participants are treated with lorlatinib. With 100 participants, any AE rate can be estimated with the maximum standard error of 0.05. All participants who receive at least 1 dose of lorlatinib will be included in the safety and antitumor activity analyses, unless otherwise specified.

Analysis of Primary Endpoint

AEs will be graded by the Investigator according to the CTCAE version 4.03 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The focus of AE summaries will be on treatment-emergent adverse events (TEAEs), those with an initial onset or increasing in severity after the first dose of study medication to at most 35 days post last dosing date or the date of initiation of a new anticancer therapy. The number and percentage of participants who experienced any AE, serious adverse event (SAE), treatment-related AE, and treatment-related SAE will be summarized.

Additional Safety Analyses

Other safety parameters, including study treatment exposure, laboratory, electrocardiogram (ECG), vital signs measurements, dose reductions due to AEs, and temporary and permanent discontinuations due to AEs, will be summarized descriptively.

Analysis of Secondary Endpoints

The following analyses of response will be performed according to the Investigator assessment using RECIST version 1.1.

ORR

ORR is defined as the percent of participants with best overall response as confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1. ORR will be provided along with the corresponding 95% CI based on Wilson's Score Method.

IC-ORR

IC-ORR is defined as the percent of participants with intracranial response (ie, best overall intracranial response as confirmed CR or confirmed PR considering only intracranial lesions) relative to participants with CNS metastases at study entry. IC-ORR will be provided along with the corresponding 95% CI based on Wilson's Score Method.

DoR

DoR is defined as the time from the first documentation of objective tumor response (confirmed CR or confirmed PR) to the first documentation of disease progression or death due to any cause, whichever occurs first. For participants whose responses proceed from PR to CR, the onset of PR is taken as the onset of response. DoR will be summarized in the population of participants with a confirmed CR or confirmed PR using the Kaplan Meier method and will be displayed graphically where appropriate. The median event time (if appropriate) and 2-sided 95% CI for the median will be provided. Censoring for DoR will be described in the statistical analysis plan (SAP). In case the number of participants with progressive disease (PD) after a confirmed CR or confirmed PR is small, the use of Kaplan Meier method may be limited and descriptive statistics may be provided.

IC-DoR

IC-DoR is defined as the time from the first documentation of an intracranial objective response in the subgroup of participants with brain metastasis at baseline. Analyses similar to DoR will be repeated for IC-DoR considering participants with intracranial response (ie, best overall intracranial response as confirmed CR or confirmed PR considering only intracranial lesions).

End of Study

The end of study is defined as 1 year after the "last participant first visit" (LPFV) date in the study.

SCHEDULE OF ACTIVITIES

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

The Investigator may schedule visits (unplanned visits) in addition to those listed on the Schedule of Activities, in order to conduct evaluations or assessments required to protect the wellbeing of the participant.

Visit Identifier	Screening	Cycle 1 (28 days)	Visit on Day 1 of Every Cycle	End of Treatment	Follow-Up[8]
Visit Window	**≤28 days**	**Day 1**	**±2 days**	**±7 days**	
Informed consent[1]	X				
Tumor history	X				
Medical history	X				
Physical examination and vital signs	X	X	X	X	
Body weight		X	X	X	
ECOG performance status	X	X	X	X	
Contraception check[2] (as appropriate)		X	X	X	X
Laboratory					
Hematology	X	(X)	X	X	
Blood chemistry	X	(X)	X	X	
Lipids	X	(X)	X	X	
Pregnancy test[3]	X	X	X	X	X
Cardiac Monitoring					
12-Lead ECG[4]	X	(X)	X (every cycle up to Cycle 5)	X	
Treatment					
Lorlatinib		Orally once daily, continuously			
Tumor Assessments					
CT or MRI imaging[5]	X		X (every 12 weeks ±1 week)	X	
Other Clinical Assessments					
Serious and non-serious AEs[6]	X	X	X	X	X
Concomitant medications and non-drug supportive interventions[7]	X	X	X	X	X

(X): No need to repeat if assessment performed within 7 days prior to Cycle 1 Day 1.
Abbreviations: AE=adverse event; CAP=chest abdomen pelvis; CRF=case report form; CT=computed tomography; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; NCI=National Cancer Institute; QTc=QT interval corrected for heart rate; RECIST=Response Evaluation Criteria in Solid Tumor; SAE=serious adverse event.

1. Informed consent must be obtained prior to undergoing any study-specific procedures that are not considered standard of care.
2. Contraceptive check: participant may be contacted by phone to confirm contraception is still appropriate per the protocol.

3. Pregnancy test: for female participants of childbearing potential, a serum or urine pregnancy test will be performed at Screening and at the Cycle 1 Day 1 visit. Results must be available before investigational product administration. Pregnancy tests will be also routinely repeated at every cycle during the active treatment period, at the end of treatment, at the short-term follow-up visit, and additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected.
4. 12-lead ECGs: 3 consecutive 12-lead ECGs pre-dose will be performed approximately 2 minutes apart to determine mean PR interval and QTc interval at baseline (screening and Cycle 1 Day 1 if the ECG at screening is performed more than 7 days before Cycle 1 Day 1) and single ECGs will be performed at Day 1 of every cycle up to Cycle 5 and at the end of treatment. Additional ECGs may be collected as clinically indicated.
5. Tumor assessment: tumor assessments will include all known or suspected disease sites. CT or MRI scans of CAP and MRI of the brain will be performed at Screening and repeated every 12 weeks (±1 week). For all tumor assessments, the method of assessment that was used at Screening should be the same method used throughout the study. Responses will be confirmed ≥4 weeks after first occurrence of response, according to RECIST version 1.1 criteria. Tumor assessment should be repeated at the end of treatment if more than 6 weeks have passed since the last evaluation.
6. AE assessments: AEs should be documented and recorded into the electronic CRF at each visit using NCI CTCAE version 4.03. For AEs and SAEs, the active collection period to Pfizer or its designated representative begins from the time that the participant provides informed consent, through and including at least 28 calendar days and no more than 35 days after the last administration of the investigational product. If a participant begins a new anticancer therapy, the reporting period for non-serious AEs ends at the time the new treatment is started. SAEs and Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.
7. Concomitant medications and non-drug supportive interventions: all concomitant medications and non-drug supportive interventions should be recorded in the CRF from 28 days prior to start of study treatment and up to at least 28 days and no more than 35 days after the last dose of study treatment.
8. Follow-up: at least 28 days, and no more than 35 days after discontinuation of treatment, participants will return to undergo contraception check, pregnancy test, review of concomitant medications, AE assessments, and review for resolution of any treatment-related toxicity.

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1. INTRODUCTION

1.1. Mechanism of Action/Indication

Lorlatinib is a third-generation, oral, reversible, ATP-competitive, macrocyclic TKI of ALK and ROS1. Compared with second-generation inhibitors, lorlatinib was specifically designed to penetrate the CNS and to overcome known secondary resistance mutations in the ALK tyrosine kinase domain.

1.2. Background and Rationale

Lung cancers that harbor chromosomal rearrangements of ALK constitute about 3-5% of NSCLCs and are highly responsive to small-molecule TKIs that target ALK. Standard treatment of patients with advanced ALK-positive NSCLC has recently shifted from sequential crizotinib followed by more potent second-generation ALK TKIs to front-line second-generation TKIs. Whereas most patients derive clinical benefit from second-generation ALK TKIs, acquired resistance invariably develops and leads to clinical relapse.[1]

Preclinical studies demonstrate that lorlatinib is more potent than earlier-generation TKIs against nonmutant ALK and retains potency against most known single ALK resistance mutations, including the highly refractory ALK G1202R solvent front mutation.[2]

In the pivotal single arm, multicenter Phase 2 study, treatment with lorlatinib showed clinically relevant response rates and durable response in patients with ALK-positive NSCLC who had previously received at least 1 ALK TKI, including the second-generation drugs ceritinib and alectinib.[1] In the cohort of patients previously treated with a second-generation ALK TKI (N=28), objective responses were observed in 9 patients (32%, 95% CI: 15.9-52.4). Substantial intracranial activity was also observed in these patients suffering from frequent brain metastases. The proportion of patients with objective intracranial response to lorlatinib was 55.6% (95% CI: 21.2-86.3) in patients with at least 1 measurable brain lesion at baseline (N=9). The overall and intracranial median DoR were not reached (95% CI: 4.1 months - not reached; duration of follow-up 7 months).

On the basis of pivotal Phase 1/2 Study B7461001, lorlatinib received conditional marketing authorization by the Indian Ministry of Health for the treatment of ALK fusion gene-positive unresectable advanced and/or recurrent NSCLC with resistance or intolerance to ALK TKI(s).

In view of the lack of participants in India from the Study B7461001 and of the limited number from the ongoing Phase 3 Study B7461006 (CROWN), the Indian Ministry of Health requested the Sponsor to conduct a post-approval study to obtain additional data on participants in India. The study will be conducted as a PASS.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Indian product label.

2. STUDY OBJECTIVES AND ENDPOINTS

Objective	Estimands	Endpoints
Primary		
• To evaluate the safety and tolerability of single-agent lorlatinib in participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment.	• The primary estimand is the incidence of AEs from the time of first dose to at most 35 days post last dosing date or the date of initiation of a new anticancer therapy for all participants who receive at least 1 dose of lorlatinib, regardless of dosing interruptions or dosing compliance.	• Incidence of AEs.
Secondary		
• To evaluate overall and intracranial antitumor activity of single-agent lorlatinib in participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment.	• The secondary estimand is the treatment effect of lorlatinib as assessed by the investigator from time of first dose (ORR and IC-ORR) or time of first response (DoR and IC-DoR) until progression is met, death or subsequent anticancer therapy is administered for all participants who receive at least 1 dose of lorlatinib without regard to tolerability or discontinuation from treatment.	• Confirmed ORR, confirmed IC-ORR, DoR and IC-DoR as assessed by the Investigator using RECIST version 1.1.

3. STUDY DESIGN

This is a Phase 4, open-label, multicenter, non-randomized, prospective, single arm study to evaluate the safety and tolerability of lorlatinib in adult participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment.

This study will enroll enough participants to ensure that 100 participants are treated with lorlatinib.

4. PARTICIPANT SELECTION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom the protocol intervention is considered appropriate by their health care provider.

4.1. Inclusion Criteria

Participant eligibility should be reviewed and documented by an appropriate member of the Investigator's study team before participants are included in the study.

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

1. Evidence of histologically or cytologically confirmed diagnosis of unresectable advanced and/or recurrent NSCLC that carries an ALK rearrangement, as detected by an appropriate test.

2. Disease progression or intolerance to 1 previous treatment with ALK TKI. participants may have also had prior chemotherapy for their advanced and/or recurrent disease.

3. Participants with asymptomatic CNS metastases (including participants controlled with stable or decreasing steroid use within the last 2 weeks prior to study enrollment) will be eligible.

4. Age ≥18 years.

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

6. Adequate hematologic and renal function as defined as:

    a. Absolute neutrophil count (ANC) ≥1,000/mm^3;

    b. Platelets ≥50,000/mm^3;

    c. Hemoglobin ≥8 g/dL;

    d. Estimated creatinine clearance ≥30 mL/min as calculated using the method standard for the institution.

7. Adequate liver function, including:

    a. Total serum bilirubin ≤1.5 × upper limit of normal (ULN);

    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN (≤5.0 × ULN in case of liver metastases).

8. Adequate pancreatic function, including:

    a. Serum total amylase ≤1.5 × ULN.*

    b. Serum lipase <1.5 × ULN.

    *if total amylase >1.5 × ULN, but pancreatic amylase is within the ULN, the participant may be enrolled.

9. Acute effects of any prior therapy resolved to baseline severity or to CTCAE Grade <1 except for AEs that in the Investigator's judgment do not constitute a safety risk for the participant.

10. Systemic anticancer therapy completed within a minimum of 5 half-lives of study enrollment (unless clinically meaningful tumor flare per discretion of the Investigator, in which discussion with the Sponsor is warranted).

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

12. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures.

13. Pregnancy test for females of childbearing potential negative at Screening or female participants who are not of childbearing potential (refer to Appendix 1 for definition). Male and female participants of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception from the time of Screening, throughout the study and for 3 months after the last dose of assigned treatment, 6 months if female participants.

4.2. Exclusion Criteria

Participants presenting with any of the following will not be included in the study:

1. Radiation therapy (except palliative to relieve bone pain) within 2 weeks of study enrollment. Palliative radiation (<10 fractions) must have been completed at least 48 hours prior to study enrollment. Stereotactic or small field brain irradiation must have completed at least 2 weeks prior to study enrollment. Whole brain radiation must have completed at least 4 weeks prior to study enrollment. Prior irradiation to >25% of the bone marrow.

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

3. Known prior or suspected severe hypersensitivity to study drug or any component in its formulation.

4. Active and clinically significant bacterial, fungal, or viral infection.

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

    a. Arterial disease such as cerebral vascular accident/stroke (including transient ischemic attack [TIA]), myocardial infarction, unstable angina;

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

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

6. History or known presence of interstitial fibrosis, interstitial lung disease (ILD), pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, obliterative bronchiolitis, and pulmonary fibrosis.

7. Other severe acute or chronic medical or psychiatric condition, including recent (within the past year) or active suicidal ideation or behavior, or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the participant inappropriate for enrollment in this study.

8. Evidence of active malignancy (other than current NSCLC, non-melanoma skin cancer, in situ cervical cancer, papillary thyroid cancer, ductal carcinoma in situ [DCIS] of the breast or localized and presumed cured prostate cancer) within the last 3 years prior to enrollment.

9. 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 categories described below) within 12 days prior to the first dose of lorlatinib:

   a. Known strong cytochrome (CYP)3A inducers (eg, carbamazepine, enzalutamide, mitotane, rifampin, St. John's Wort).

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

   c. Known CYP3A substrates with narrow therapeutic index, such as pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, alfentanil, fentanyl (including transdermal patch) or ergot alkaloids (ergotamine, dihydroergotamine).

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

10. Participants who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the Investigator, or participants who are Pfizer employees directly involved in the conduct of the study.

11. Participation in other studies involving investigational drug(s) (Phases 1-4) during study participation.

12. Breastfeeding female participants.

4.3. Life Style Guidelines

See Appendix 1 for mandatory contraception information.

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

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

5. STUDY INTERVENTION

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

Table 1. Study Intervention(s) Administered

ARM name	Lorlatinib 100 mg QD
Intervention name	Lorlatinib
Type	Small molecule
Dosage form	Tablet
Dose strength	25 mg
Dosage	100 mg QD
Route of administration	Oral
Sourcing	Provided centrally by the Sponsor
Packaging and labeling	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.
Current/former name(s) or alias(es)	PF-06463922/lorlatinib

Abbreviation: QD=once daily.

5.1. Allocation to Intervention/Treatment

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

5.2. Drug Supplies

5.2.1. Dosage Form(s) and Packaging

Lorlatinib (PF-06463922) will be supplied by Pfizer Global Clinical Supply for oral administration as 25 mg tablets in high-density polyethylene (HDPE) bottles with desiccant and labeled according to local regulatory requirements.

Drug supplies will be shipped to the study sites with a Drug Shipment and Proof of Receipt form. This form will be completed and filed, as directed on the bottom of the Drug Shipment and Proof of Receipt form. The Investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

5.3. Administration

The product will be administered in accordance with the label.

The recommended dosage of lorlatinib is 100 mg orally QD, with or without food, until disease progression, unacceptable toxicity, or participant refusal/lost to follow-up. Tablets should be swallowed whole. Tablets should not be chewed, crushed, or split. Tablets should not be taken if they are broken, cracked, or otherwise not intact. Lorlatinib should be taken at the same time each day. If a dose is missed, then the missed dose should be taken unless the next dose is due within 4 hours. Two (2) doses should not be taken at the same time to make up for a missed dose. An additional dose should not be taken if vomiting occurs after lorlatinib but the next scheduled dose should be continued. Dosing interruption or dose reduction may be required based on individual safety and tolerability.

Lorlatinib dose reduction levels are summarized below:

- First dose reduction: 75 mg taken orally QD;
- Second dose reduction: 50 mg taken orally QD.

Lorlatinib should be permanently discontinued if the participant is unable to tolerate the 50 mg dose taken orally QD. Dose modification recommendations for adverse reactions are provided in Table 2.

Table 2. Dose Modification Recommendation for Adverse Reactions of Lorlatinib

Adverse Reaction	Lorlatinib Dosing
CNS Effect	
Grade 1	Continue lorlatinib at same dose or withhold the dose until recovery to baseline. Resume lorlatinib at the same dose or at a reduced dose.
Grade 2 or Grade 3	Withhold dose until Grade 0 or 1. Resume lorlatinib at a reduced dose.
Grade 4	Permanently discontinue lorlatinib.
Hyperlipidemia	
Grade 4 hypercholesterolemia or Grade 4 hypertriglyceridemia	Withhold lorlatinib until recovery of hypercholesterolemia and/or hypertriglyceridemia to less than or equal to Grade 2. Resume lorlatinib at the same dose. If severe hypercholesterolemia and/or hypertriglyceridemia recurs, resume lorlatinib at a reduced dose.
AV block	
Second-degree AV block	Withhold lorlatinib until PR interval is less than 200 msec. Resume lorlatinib at a reduced dose.
First occurrence of complete AV block	Withhold lorlatinib until: • pacemaker placed, or • PR interval less than 200 msec. If a pacemaker is placed, resume lorlatinib at the same dose. If no pacemaker is placed, resume lorlatinib at a reduced dose.
Recurrent complete AV block	Place pacemaker or permanently discontinue lorlatinib.
ILD/Pneumonitis	
Any grade treatment–related ILD/Pneumonitis	Permanently discontinue lorlatinib.
Other adverse reactions	
Grade 1 or Grade 2	Continue lorlatinib at same dose or reduced dose.
Grade 3 or Grade 4	Withhold lorlatinib until symptoms resolve to less than or equal to Grade 2 or baseline. Resume lorlatinib at reduced dose.

Grade based on NCI CTCAE version 4.0.
Abbreviations: AV=atrioventricular; CNS=central nervous system; CTCAE=Common Terminology Criteria for Adverse Events; ILD=interstitial lung disease; NCI=National Cancer Institute.

5.4. Drug Storage

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be

documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperature since previously documented for all site storage locations upon return to business.

3. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

4. Study interventions should be stored in their original containers and in accordance with the labels.

5. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

6. Deviations from the storage requirements, including any actions taken, must be documented and reported to Pfizer upon discovery. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. It will not be considered a protocol deviation if Pfizer approves the use of the study intervention after the temperature excursion. Use of the study intervention prior to Pfizer approval will be considered a protocol deviation. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the investigational product manual.

5.5. Drug Accountability

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records). All study interventions will be accounted for using an investigational product accountability form/record. Further guidance and information for the final disposition of unused study interventions are provided in the investigational product manual.

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

5.6. Concomitant Treatments

The use of permitted concomitant medication must be in accordance with the study drug label.

All concomitant medications and non-drug supportive interventions should be recorded in the CRF from 28 days prior to start of study treatment and to at least 28 days and no more than 35 days after the last dose of study treatment.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with reason for use and dates of administration including start and end dates.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

5.6.1. Prohibited Concomitant Treatments

Concomitant treatment considered necessary for the participant's wellbeing may be given at discretion of the treating physician. Prior to giving any concomitant medication, the following lorlatinib drug interaction information should be considered.

Lorlatinib is a substrate of CYP3A. This is supported by drug interaction studies in healthy volunteers, in which lorlatinib exposure was decreased by a strong CYP3A inducer (rifampin) and increased by a strong CYP3A inhibitor (itraconazole).

Thus, the following cautions are provided:

- Lorlatinib metabolism may be inhibited by strong CYP3A inhibitors leading to a potential increase in lorlatinib toxicities. Concomitant administration of lorlatinib with strong CYP3A inhibitors (eg, boceprevir, cobicistat, clarithromycin, conivaptan, diltiazem, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir, nelfinavir, paritaprevir, posaconazole, ritonavir alone and with elvitegravir or indinavir or lopinavir or paritaprevir or ombitasvir or dasabuvir or saquinavir or tipranavir, telaprevir and voriconazole) may increase lorlatinib plasma concentrations. Grapefruit products may also increase lorlatinib plasma concentrations and should be avoided. An alternative concomitant medicinal product with less potential to inhibit CYP3A should be considered. If a strong CYP3A inhibitor must be co-administered, the starting lorlatinib dose of 100 mg QD should be reduced to 75 mg dose QD. In participants who have had a dose reduction to 75 mg orally QD due to adverse reactions and who initiate a strong CYP3A inhibitor, reduce lorlatinib dose to 50 mg orally QD. If concurrent use of the strong CYP3A inhibitor is discontinued, lorlatinib should be resumed at the dose used prior to the initiation of the strong CYP3A inhibitor and after a washout period of 3 to 5 half-lives of the strong CYP3A inhibitor. The participant should be closely monitored for safety and reduction of the lorlatinib dose if necessary.

In the B7461011 study, in which lorlatinib was co-administered with rifampin, significant increases in AST and ALT were observed. In subsequent studies in cynomolgus monkeys, lorlatinib in combination with carbamazepine demonstrated similar AST and ALT elevations as well.

Thus, the following clinical guidance is provided:

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

In vivo results show that lorlatinib 100 mg QD at steady state is a moderate inducer of CYP3A. In addition, a drug interaction study conducted in NSCLC participants indicated that lorlatinib is a moderate inducer of P-gp.

Thus, the following clinical guidance is provided:

- Lorlatinib is a net moderate inducer of CYP3A at steady state. Thus, concurrent administration of lorlatinib with CYP3A substrates with narrow therapeutic indices (NTIs), including but not limited to alfentanil, ciclosporin dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus and tacrolimus, should be avoided since the concentration of these medicinal products may be reduced by lorlatinib. However, if it is absolutely necessary to use, Sponsor approval is required and the dose of the CYP3A substrate may need to be increased. The narrow NTI CYP3A substrate should be started only after at least 14 days of continuous lorlatinib dosing. If there is a change in the lorlatinib dosing regimen such as a dosing interruption or dose reduction, the administration of the NTI CYP3A substrate should be stopped and resumed at a readjusted dose only after at least 14 days of resumed lorlatinib dosing.

- Lorlatinib is a net moderate inducer of P-gp at steady state. The concurrent use of drugs which are P-gp substrates with NTI, such as digoxin is not permitted at study entry. The use of these drugs during the study is not recommended and alternate medications should be considered. If absolutely necessary to use during the study, it should be initiated following sponsor approval, and be used then with caution.

Other Antitumor or Experimental Drugs

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

Hematopoietic Growth Factors

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

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

5.6.2. Permitted Concomitant Treatments

Bisphosphate Therapy

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

Lipid-Lowering Therapy

Since statins can be metabolized or inhibited by the same CYP450 pathways as lorlatinib (Appendix 2), pitavastatin or pravastatin followed by rosuvastatin should be the agents to use concomitantly with lorlatinib since they are the least involved with the CYP450 enzyme systems. However, no clinical drug-drug interactions have been formally studied with lorlatinib and careful monitoring is advised.

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

Radiotherapy

- Palliative radiotherapy on study is permitted for the treatment of painful bony lesions providing the lesions were known at the time of study entry and the Investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of lorlatinib with radiotherapy, lorlatinib treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment after recovery from acute radiation toxicities to baseline.

Surgery

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

6. STUDY PROCEDURES

6.1. Screening

All participants being considered for the study and eligible for screening must sign an informed consent for the study before completing any study-specific procedures. Participants will be screened within 28 days prior to first dosing of lorlatinib to confirm that they meet the eligibility criteria for the study. The required screening assessments are summarized in the Schedule of Activities and Section 7 Assessments.

6.2. Study Period

For study treatment period procedures, see Schedule of Activities and Section 7 Assessments.

6.3. Follow-up Visit

At least 28 days, and no more than 35 days after discontinuation of treatment, participants will return to undergo contraception check, pregnancy test, review of concomitant medications, AE assessments, and review for solution of any treatment-related toxicity.

6.4. Participant Withdrawal

- Participants who request to discontinue 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 participant specifically withdraws consent for any further contact with him/her or persons previously authorized by participant to provide this information. Participants should notify the Investigator of the decision to withdraw consent from future follow-up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the Investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page.

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant as noted above. Lost to follow-up is defined by the inability to reach the participant after a minimum of 3 documented phone calls, faxes, or emails as well as lack of response by participant to 1 registered mail letter. All attempts should be documented in the participant's medical records. If it is determined that the participant has died, the site will use permissible local methods to obtain the date and cause of death. If Investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the Investigator may use a Sponsor retained third-party representative to assist site staff with obtaining participant'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 participant remains lost to follow-up, then the last known alive date as

determined by the Investigator should be reported and documented in the participant's medical records.

Participants 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.

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

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

7. ASSESSMENTS

7.1. Antitumor Activity Assessments

Tumor assessments will include all known or suspected disease sites. Computed tomography (CT) or magnetic resonance imaging (MRI) scans of chest abdomen pelvis (CAP) and MRI of the brain will be performed at Screening. Gadolinium contrast enhanced MRI must be used for assessment of CNS lesions with contingent slices of 1 mm for lesions 5 mm to 10 mm in size, 5 mm for lesions greater than 10 mm. For all tumor assessments, the method of assessment that was used at Screening should be the same method used throughout the study. CT and MRI scans to be done at every 12 weeks ±1 week till the end of treatment. Tumor assessment should be repeated at the end of treatment if more than 6 weeks have passed since the last evaluation. Moreover, radiological tumor assessments will be conducted whenever disease progression is suspected (eg, symptomatic deterioration).

Assessment of response will be made using RECIST version 1.1 (Appendix 3). Confirmation of response will be required at least 4 weeks after initial response is observed.

All participants' files and radiologic images must be available for source verification.

7.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

7.2.1. Physical Examination

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

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

7.2.2. Electrocardiogram

- ECG will be obtained as outlined in the Schedule of Activities using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

- PR interval prolongation and AV block have been reported in participants receiving lorlatinib. If at any time the mean PR interval is prolonged (≥200 msec) or QTc is prolonged (≥470 msec), the ECGs should be re-evaluated by a qualified person at the institution for confirmation.

- ECG values of potential concern are listed in Appendix 4. Dose modifications for AV block is provided in Table 2.

7.2.3. ECOG Performance Status

Refer to Appendix 5 for ECOG PS criteria.

7.2.4. Clinical Safety Laboratory Assessments

The required laboratory tests are listed in Appendix 6.

- Hematology and blood chemistry will be collected at the time points described in the Schedule of Activities and analyzed at local laboratories. They may also be performed when clinically indicated. Local laboratory certification(s) and reference ranges should be provided to the Sponsor prior to study participant screening activity.

7.2.5. Pregnancy Testing

Pregnancy tests may be urine or serum tests but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in woman of childbearing potential (WOCBP) at the times listed in the Schedule of Activities. Following a negative pregnancy test result at Screening, appropriate contraception must be commenced, and a second negative pregnancy test result will be required at Cycle 1 Day 1 prior to the participant's receiving the study intervention. Pregnancy tests will also be repeated at every cycle during the active treatment period, at the end of treatment, and at the short-term follow-up visit to be performed at least 28 days and no more than 35 days after the last dose. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or

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

In the case of a confirmed pregnancy, the participant will be withdrawn from study medication and from the study.

Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

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

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE. The Investigator is required to assess causality. 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.

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.

8.2. Reporting Period

For AEs and SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the participant provides informed consent, which is obtained prior to the participant's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including at least 28 calendar days and no more than 35 days after the last administration of the investigational product. SAEs occurring to a participant after the active reporting period has ended should be reported to the Sponsor 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 study drug are to be reported to the Sponsor.

If a participant begins a new anticancer therapy, the AE reporting period for nonserious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of An Adverse Event

An AE is any untoward medical occurrence in a clinical investigation participant 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 symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

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

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong drug, by the wrong participant, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the AE CRFs and on the SAE form when appropriate. In the event of medication dosing error, the Sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

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

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, the medication error and, if applicable, any associated AE(s) are captured on an AE CRF page (refer to Section 8 Adverse Event Reporting section for further details).

8.4.1. Treatment of Overdose

For this study, any dose of lorlatinib greater than 100 mg within a 24-hour time period will be considered an overdose. Sponsor does not recommend specific treatment for an overdose. There is no antidote for lorlatinib.

In the event of an overdose, the Investigator should:

1. Contact the medical monitor immediately.
2. Closely monitor the participant for any AE/SAE and given the dose dependent effect on PR interval, ECG monitoring is recommended.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to safety only when associated with a SAE.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- 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 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 reporting as an AE.

8.6. Serious Adverse Event

An SAE 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.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an SAE with Common Terminology Criteria (CTC) Grade 5 (see Section 8.8 Severity Assessment).
- Lack of efficacy should be reported as an AE when it is associated with an SAE.

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. The important medical event should be reported as serious, if it is determined that the event may jeopardize the participant or may require intervention to prevent 1 of the other AE outcomes.

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.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the Investigator as described in previous sections, and will be handled as SAEs in the safety database (see section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Case of Drug-Induced Liver Injury

Abnormal values in AST and/or ALT levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- participants with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 × ULN concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For participants with preexisting ALT or AST or total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For participants with 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).

- Concurrent with:

    - For participants with preexisting values of total bilirubin above the normal range: Total bilirubin level increased by 1 × ULN or ≥3 × ULN (whichever is smaller).

The participant should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected.

Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal liver function tests. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to 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 should be 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 persistent pre-treatment laboratory abnormality);
- Social admission (eg, participant 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 participant;
- Admission exclusively for the administration of blood products.

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

8.8. Severity Assessment

AEs will be graded by the Investigator according to the CTCAE version 4.03.

Grade	Clinical Description of Severity
1	Mild adverse event
2	Moderate adverse event
3	Severe adverse event
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

8.9. 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 in the CRF, as appropriate, 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 (see Section 8.13 Reporting Requirements). 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, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For investigational products and for marketed products, an EDP occurs if:

1. 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).

2. A male participant 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 study participant or study participant's partner becomes or is found to be pregnant during the study participant's treatment with the investigational product, the Investigator must submit this information to the Pfizer drug safety unit on a SAE Report Form and EDP supplemental form, regardless of whether an SAE has occurred. In addition, the Investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a participant reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) 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 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, 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 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 investigational product.

Additional information regarding the EDP may be requested by the Investigator. 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 study participant with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Withdrawal Due to Adverse Events (See Also Section on Participant Withdrawal)

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

When a participant withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study participant or legally acceptable representative. In addition, each study participant or legally acceptable representative will be questioned about AEs.

8.13. Reporting Requirements

8.13.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of Investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDP and exposure via breastfeeding cases.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study participant initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the Investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an Investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.13.2. Non-serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.13.3. Sponsor Reporting Requirements to Regulatory Authorities

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

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in an SAP, which will be maintained by the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

The primary objective of the study is to evaluate the safety and tolerability of single-agent lorlatinib in participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment.

The secondary objective of the study is to evaluate overall and intracranial antitumor activity of single-agent lorlatinib in participants with unresectable advanced and/or recurrent ALK-positive NSCLC with resistance or intolerance to at least 1 prior ALK inhibitor treatment.

9.1.1. Estimands

The primary estimand is the incidence of Adverse Events from the time of first dose to at most 35 days post last dosing date or the date of initiation of a new anticancer therapy for all participants who receive at least one dose of lorlatinib, regardless of dosing interruptions or dosing compliance.

The secondary estimand is the treatment effect of lorlatinib as assessed by the investigator from time of first dose (ORR and IC-ORR) or time of first response (DoR and IC-DoR) until progression is met, death or subsequent anticancer therapy is administered for all participants who receive at least one dose of lorlatinib without regard to tolerability or discontinuation from treatment.

9.2. Sample Size Determination

This study will enroll enough participants to ensure that 100 participants are treated with lorlatinib. With 100 participants, any AE rate can be estimated with the maximum standard error of 0.05. All participants who receive at least 1 dose of lorlatinib in this study will be included in the safety and antitumor activity analyses unless otherwise specified.

9.3. Data Sources

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

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

9.4. Antitumor Activity Analysis

All antitumor activity analyses will be performed on the safety set. Participants with inadequate baseline or no follow-up assessments will be considered as non-responders.

9.4.1. Analysis of Primary Endpoint

Not applicable.

9.4.2. Analysis of Secondary Endpoints

The following analyses of response will be performed according to the Investigator assessment using RECIST version 1.1.

ORR

ORR is defined as the percent of participants with best overall response as confirmed CR or confirmed PR according to RECIST version 1.1. ORR will be provided along with the corresponding 95% confidence interval based on Wilson's Score Method.

IC-ORR

IC-ORR is defined as the percent of participants with intracranial response (ie, best overall intracranial response as confirmed CR or confirmed PR considering only intracranial lesions) relative to participants with CNS metastases at study entry. IC-ORR will be provided along with the corresponding 95% CI based on Wilson's Score Method.

DoR

DoR is defined as the time from the first documentation of objective tumor response (confirmed CR or confirmed PR) to the first documentation of disease progression or death due to any cause, whichever occurs first. For participants whose responses proceed from PR to CR, the onset of PR is taken as the onset of response. DoR will be summarized in the population of participants with a confirmed CR or confirmed PR using the Kaplan Meier method and will be displayed graphically where appropriate. The median event time (if appropriate) and 2-sided 95% CI for the median will be provided. Censoring for DoR will be described in the SAP. In case the number of participants with PD after a confirmed CR or confirmed PR is small, the use of Kaplan Meier method may be limited and descriptive statistics may be provided.

IC-DoR

IC-DoR is defined as the time from the first documentation of an intracranial objective response in the subgroup of participants with brain metastasis at baseline. Analyses similar to DoR will be repeated for IC-DoR considering participants with intracranial response (ie, best overall intracranial response as confirmed CR or confirmed PR considering only intracranial lesions).

9.5. Analysis of Other Endpoints

Not applicable.

9.6. Safety Analysis

All safety analysis will be conducted on the safety set.

Primary Endpoint

AEs will be graded by the Investigator according to the CTCAE version 4.03 and coded using the MedDRA. The focus of AE summaries will be on TEAEs, those with an initial onset or increasing in severity after the first dose of study medication up to at most 35 days post last dosing date or the date of initiation of a new anticancer therapy. The number and percentage of participants who experienced any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized.

Adverse events leading to death or discontinuation of study treatment, events classified as NCI CTCAE version 4.03 Grade ≥3, study drug-related events, SAEs, dose reductions due to AEs, and temporary and permanent discontinuations due to AEs will be summarized.

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

Study Treatment Exposure

Drug exposure will be summarized using descriptive statistics. The number and percentage of participants with drug interruptions and the corresponding reasons will be summarized. The number and percentage of participants with dose reductions and the corresponding reasons will also be summarized.

Laboratory Abnormalities

Laboratory test results will be graded according to NCI CTCAE version 4.03. Data will be summarized by the type of laboratory test. Summary of laboratory abnormalities will be presented by maximum CTCAE grade. For laboratory tests without an NCI CTCAE grade definition, results will be categorized as normal (within normal ranges), abnormal, or not done. Shift tables will be provided to examine the distribution of laboratory abnormalities.

Vital Signs

Vital signs data will be summarized using descriptive statistics (mean, standard deviation, median, quartiles, minimum, and maximum) of actual values and change from baseline for each nominal visit over time (ie, unscheduled assessments will be excluded).

Electrocardiograms

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

QT intervals will be corrected for heart rate using standard correction factors (ie, Fridericia's [default correction], Bazett's [if necessary], and possibly a study-specific factor, as appropriate). However, safety assessments as to QTc prolongation will be based on the Fridericia's correction formula. Data will be summarized and listed for QT, HR, RR, PR, QRS, QTc.

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

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits 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 is 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.

The study site may be subject to review by the Institutional Review Board (IRB)/Ethics Committee (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.

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

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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

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

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is 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 participant's chart in the hospital or the physician's office. In these cases, data collected on the CRFs must match the data in those charts.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating participants (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Council for Harmonisation (ICH), according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

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

12. ETHICS

12.1. Institutional Review Board (IRB)/Ethics Committee (EC)

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 participants. 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 legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008) and Schedule Y, Drug and Cosmetics Act 1940 and Rules 1945.

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local India regulatory requirements and laws.

12.3. Participant Information and Consent

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

The personal data will be stored at the study site in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the

study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data is compiled for transfer to Pfizer and other authorized parties, participant names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study participants. The study site will maintain a confidential list of participants who participated in the study linking their numerical code to the participant's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of participant personal data consistent with applicable privacy laws.

The informed consent documents 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 must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

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

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

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

12.4. Participant Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. 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 Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF STUDY

13.1. End of Study in Participating Country

End of study in participating country is defined as 1 year after the LPFV date in the study.

At the end of study, participants who are on treatment and benefiting from lorlatinib treatment will be moved to commercially available lorlatinib (if considered appropriate by the Investigator) as soon as feasible.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, drug safety problems, or at the discretion of Pfizer.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating participants 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 trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), www.ctri.nic.in (Clinical Trials Registry-India) and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov

Pfizer posts clinical trial Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

15.2. Publications by Investigators

Pfizer has no objection to publication by investigator of any information collected or generated by investigator, whether or not the results are favorable to the investigational drug.

However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are 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 (other than the Study results themselves) before disclosure.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all centers. 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, investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, 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 Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol 2018;19(12):1654-67.

2. Gainor JF, Dardaei L, Yoda S, et al. Molecular Mechanisms of Resistance to First- and Second-Generation ALK Inhibitors in ALK-Rearranged Lung Cancer. Cancer Discov 2016;6(10):1118-33.

3. Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther 2006;80(6):565-81.

4. Miller M. "What Are the Effects of Statins on Triglycerides and What Are the Results of Major Outcomes Studies?" 2009 Mar 12; http://www.medscape.org/viewarticle/589010.

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7. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix 1. Contraceptive Guidance

Definition

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

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

Women in the following categories are not considered WOCBP:

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

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

      Note: Documentation for any of the above conditions can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.
3. Postmenopausal female:
    - A postmenopausal state is defined as age 60 or older or no menses for 12 months without an alternative medical cause.
        - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT.
    - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Contraception – For Women

Female participants must use highly effective contraception while taking study intervention and for at least 6 months after stopping study intervention.

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

Highly effective methods that have low user dependency includes:

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

Contraception – For Men

Male participants must use a condom while taking study intervention and for at least 3 months after stopping study intervention.

Appendix 2. Pharmacokinetic Properties of Statins and Lipid Lowering Agents

The PK properties of statins and lipid lowering agents are provided in Table 3 and Table 4, respectively.

Table 3. Pharmacokinetic Properties of Statins

Generic Name	Pitavastatin	Pravastatin	Rosuvastatin	Atorvastatin	Simvastatin	Lovastatin	Fluvastatin
Metabolism[†]	++	+	+	+++	+++	+++	+++
Metabolizing CYP enzyme (of lactone or acid form)	(2C9)	(3A4)	2C9 (2C19)	3A4 (2C8)	3A4 2C8	3A4 2C8	2C9
Inhibitor of CYP3A4[‡]	-	-	+	+	+	+	+
Inhibitor of CYP2C9[‡]	-	-	(+)	-	-	-	+
Triglyceride lowering effect	22%-31%[**]	11%-14%[*]	17%[*]	14%-19%[*]	10%-14%[*]	13%[*]	5%[***]

Adapted from Neuvonen et al, 2006.[3]
Parentheses indicate minor significance.
[†]Three (3) plus signs indicate extensively metabolized, and 1 plus sign indicates limited metabolism, eliminated mainly unchanged.
[‡]A plus sign indicates yes, and a minus sign indicates no.
[*]Baseline TG 100-200 mg/dL; Effect of Statins vs Placebo on Triglyceride Levels in 10 Primary and Secondary Placebo-Controlled Outcome Trials table in Miller 2009.[4]
[**]Baseline TG ≥150 mg/dL; Kajinami et al, 2003.[5]
[***]Schaefer et al, 2004.[6]
Abbreviations: CYP=cytochrome P450; TG=triglyceride.

Table 4. Pharmacokinetic properties of Lipid Lowering Agents

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

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

Appendix 3. RECIST Version 1.1 Tumor Assessment Criteria[7]

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

1. Measurable Lesions

   Lesions that can be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

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

2. Non-measurable Lesions

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

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

3. Special Considerations Regarding Specific Lesions

   Bone lesions

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

- Blastic bone lesions are non-measurable.

Cystic lesions

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

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

Lesions with prior local treatment

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

Solitary lesions

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

Recording Tumor Measurements

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

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

One (1) exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of ≥15 mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

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

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

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

- CR: disappearance of all target lesions.
- PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- PD: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered a sign of progression.
- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "0" on the CRF.

Non-Target Lesions

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

Response in non-target lesions is defined as follows:

- CR: disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

Cytology, Histology

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

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

New Lesions

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

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up.

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

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

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

Confirmation of Tumor Response

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

Determination of Overall Response by RECIST Version 1.1

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

Table 5. Response Evaluation Criteria in Solid Tumors

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

Abbreviations: CR=complete response, PR=partial response, SD=stable disease, PD=progressive disease, NE=none-evaluable

Best Overall Response

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

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

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions.

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

Appendix 4. ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as AEs

- Marked sinus bradycardia (rate <40 bpm) lasting minutes.
- New PR interval prolongation >200 msec.
- New prolongation of QTcF to >470 msec (absolute) or by ≥60 msec from baseline.
- New onset atrial flutter or fibrillation, with controlled ventricular response rate, ie, rate <120 bpm.
- New onset Type I second-degree (Wenckebach) AV block of >30 seconds' duration.
- Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.

ECG Findings That May Qualify as SAEs

- QTcF prolongation >500 msec.
- New ST-T changes suggestive of myocardial ischemia.
- New onset left bundle branch block (QRS >120 msec).
- New onset right bundle branch block (QRS >120 msec).
- Symptomatic bradycardia.
- Asystole:
  - In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  - In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  - Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (rate <40 bpm), accelerated idioventricular rhythm (40< x <100), and monomorphic/polymorphic ventricular tachycardia >100 bpm (such as torsades de

pointes).

- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

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

The enumerated list of major events of potential clinical concern are recommended as "alerts" and not to be considered as all inclusive of what to be reported as AEs/SAEs.
Abbreviations: AE=adverse event; AV=atrioventricular; ECG=electrocardiogram; PVC=premature ventricular complex; QTcF=QT interval calculated using Fridericia's correction factor; SAE=serious adverse event.

Appendix 5. ECOG Classification of Performance Status

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

Appendix 6. Clinical Laboratory Tests

The laboratory tests detailed in Table 6 will be performed by the local laboratory and must be performed in fasted condition. Investigators must document their review of each laboratory safety report.

Pregnancy testing:

- Refer to Section 4.1 Inclusion Criteria for screening pregnancy criteria.
- For details of timing of recommended pregnancy testing see Section 7.2.5.

Table 6 Protocol Required Safety Laboratory Assessments

Hematology	Clinical Chemistry[1]	Other Tests
Platelet count Hemoglobin WBC count with differential: Neutrophils[2] Lymphocytes[2] Monocytes[2] Eosinophils[2] Basophils[2]	BUN or urea Creatinine Glucose (fasting) Uric acid Potassium Sodium Total calcium Magnesium AST ALT Alkaline phosphatase Albumin Total bilirubin Phosphorus or phosphate Serum total amylase[3] Serum lipase	Highly sensitive serum or urine hCG pregnancy test (as needed for women of childbearing potential). Lipids: total cholesterol, LDL,[4] HDL, and triglycerides.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRF=case report form; hCG=human chorionic gonadotropin; HDL=high-density lipoprotein; INR=international normalized ratio; LDL=low-density lipoprotein; SAE=serious adverse event; ULN=upper limit of normal; WBC=white blood cell; WOCBP=woman of childbearing potential.

1. All events of ALT ≥3 × ULN and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and INR >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE.
2. Values in percentages (%) are acceptable.
3. Pancreatic isoenzyme required if serum total amylase not within normal limits per local institutional ranges.
4. A measured LDL value is preferable instead of calculated LDL. If LDL value is calculated from Friedewald equation, this can be considered only in absence of the following circumstances: plasma dysbetalipoproteinemia (Type III hyperlipoproteinemia).