X396-CLI-301

eXALT3: Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

PROTOCOL NUMBER:	X396-CLI-301
TRIAL DRUG:	Ensartinib (X-396)
IND NUMBER:	111,695
EUDRACT NUMBER:	2015-004147-40
SPONSOR:	Xcovery Holdings Inc 11780 US Highway 1 Suite 202 Palm Beach Gardens, FL 33408
SPONSOR REPRESENTATIVE:	
GLOBAL MEDICAL MONITOR:	
ORIGINAL PROTOCOL DATE:	28 September 2015
PROTOCOL AMENDMENT 5.0 DATE:	11 May 2020

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Principal Investigator Signature Form

TITLE: eXALT3: Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

Protocol Number:	X396-CLI-301
Protocol Amendment Date	11 May 2020
IND Number:	111,695
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Study Sponsor:	Xcovery

PRINCIPAL INVESTIGATOR COMMITMENT:

Principal Investigator (Name Printed or Typed)	**Principal Investigator Signature**	**Date**

Clinical Trial Signature Approval Page

TITLE: eXALT3: Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive NonSmall Cell Lung Cancer (NSCLC) Patients Protocol Number: X396-CLI-301

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Study Sponsor:	Xcovery

Medical Monitor (Name Printed or Typed)	**Medical Monitor Signature**	**Date**

Sponsor Representative (Name Printed or Typed)	**Sponsor Representative Signature**	**Date**

Summary of Changes: eXALT3: Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

Amendment #: 5.0 (COVID-19) Amendment Date: 11May2020	**Revision(s) Made**
Entire Protocol	Reversioned, re-dated and minor editorial changes throughout document.
Synopsis - Objectives	Moved the following from Exploratory to Secondary: To compare the quality of life (QoL) in patients receiving ensartinib vs. crizotinib.
Synopsis – Efficacy Endpoints	Moved the following from Exploratory to Secondary: Patient reported time to deterioration (TTD) as measured by the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale (LCSS), patient reported health-related quality of life (HRQoL) as measured by the EORTC C30/LC13 QoL questionnaire and LCSS,
Synopsis – Statistical Methodology	Added the bolded to the following sentence: An interim analysis will be performed after approximately 75% of the planned PFS events per IRR have occurred (**around** 143 of 190 total events) in ITT population.
Synopsis – Statistical Methods	Added the bolded to the following sentence: The interim analysis will be performed after **approximately** the first 143 events have been observed and the primary endpoint of PFS will be tested at a 2-sided alpha level of 0.019.
2.2 Secondary Objectives and 2.3 Exploratory Objectives	Moved the following from Exploratory Objectives to Secondary Objectives: To compare the quality of life (QoL) in patients receiving ensartinib vs. crizotinib.
3.2 Secondary Efficacy Endpoints and 3.3 Exploratory Endpoints	Moved the following from Exploratory Endpoints to Efficacy Endpoints: Patient reported time to deterioration (TTD) as measured by the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale (LCSS) Patient reported health-related quality of life (HRQoL) as measured by the EORTC C30/LC13 QoL questionnaire and LCSS
9.1 Overview	Added the following sentence: Very unsual circumstances, e.g. global disasters or pandemics including COVID-19 ongoing one, may prevent full compliance to visit schedule, however, during normal periods every effort should be made to comply.

Summary of Changes: eXALT3: Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

Amendment #: 5.0 (COVID-19)
Amendment Date: 11May2020

	Revision(s) Made
9.3 Trial Treatment Period	Added the bolded to the following sentence: Patients will visit the study center on approximately Day 15 of Cycle 1 and Day 1 of each cycle (i.e., every 28 ± 3 calendar days **or every 12 weeks ± 1 week starting at Cycle 19 due to impact of COVID-19 pandemic**) and at other times as specified.
9.4 End of Trial Treatment	Added the bolded to the following sentences: For patients who discontinue treatment without radiographic progression per RECIST 1.1 (e.g., in patients who discontinue treatment for clinical disease progression or adverse reactions), disease assessments should continue approximately every 8 weeks **(or every 12 weeks ± 1 week starting at Cycle 19 due to impact of COVID-19 pandemic)** after study treatment until radiographic disease progression or alternate therapy is given. Note: patients that end treatment for reasons other than disease progression should continue to be followed every 8 weeks **(or every 12 weeks ± 1 week starting at Cycle 19 due to impact of COVID-19 pandemic)**.
9.4 End of Trial Treatment	Deleted the lined out in the following sentences: After the completion of study treatment, patients will be followed for survival. This should be done approximately ~~every 3 months for the first year after the end of treatment and then approximately~~ every 6 months. Note: patients that end treatment for reasons other than disease progression should continue to be followed every 8 weeks (or every 12 weeks ± 1 week starting at Cycle 19 due to impact of COVID-19 pandemic). Once disease progression occurs per RECIST criteria, then follow for survival approximately ~~every 3 months for the first year and then approximately~~ every 6 months.
9.6 Safety Assessments	Added the following: Very unsual circumstances, e.g. global disasters or pandemics as the COVID-19 pandemic, may prevent full compliance to visit schedule. During such periods, since trial participants may not be able to come to the investigational site for protocol-specified visits, other means to access patient safety may be used, e.g. virtual visits, valid patient information from local (non-study site) healthcare facilities, PI risk assessments with the prirotity to ensure the safety of trial participants.
9.6.3.1 12-Lead Electrocardiograms	Added the following: Virtual safety assessments during COVID-19 pandemic During the COVID-19 pandemic (and as well in similar situations of global disasters) patients that cannot reach the investigational site nor a local health care

Summary of Changes: eXALT3: Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

Amendment #: 5.0 (COVID-19)

Amendment Date: 11May2020	**Revision(s) Made**
	facility to perform the above listed laboratory tests and EKG as planned by a scheduled visit by protocol could be evaluated by the investigator with a virtual visit. Before receiving study drug safety must be paramount and ensured based on patient history on drug and current symptoms and sings. Investigator and site must then document the findings in the clinical chart and consequent decision on study drug administration.
9.6.4.1 Restaging	Added the bolded to the following: Patients will be restaged at approximately 8-week intervals (approximately every 2 cycles) during trial treatment. **However, beginning at Cycle 19, the interval will increase to every 12 weeks (+/- 1 week) due to impact of COVID-19 pandemic.** For a best response of CR or PR, the response must be documented to have lasted for a minimum of 4 weeks, i.e., on 2 assessments performed at least 4 weeks apart. Patients with progressive disease or unacceptable toxicity should be discontinued from study drug unless it is thought to be in the patient's best interest to remain on treatment and this has been allowed by the Medical Monitor, as discussed elsewhere in the protocol. For patients who discontinue treatment without radiographic progression per RECIST 1.1 (e.g., in patients who discontinue treatment for clinical disease progression or adverse reactions), disease assessments should continue approximately every 8 weeks after discontinuation of study treatment until radiographic disease progression or alternate therapy is given. **As above, beginning at Cycle 19, the interval will increase to every 12 weeks (+/- 2 weeks) due to impact of COVID-19 pandemic.** The assessments that will be performed at each visit during the trial treatment period are specified in Appendix E. **In case patients cannot perform the required scan as during the COVID-19 pandemic, efforts should be made to have a scan taken at a local facility and send it to the investigational site to be then transmitted for central read. If this is not possible the scan will be skipped and recorded as a deviation and schedule will be resumed at next possible visit.**
9.6.4.2 Quality of Life Assessments	Added the following: For consented patients during unsual circumstances, e.g. global pandemics, and unable to provide quality of life assessments these will not be protocol deviations.
9.7 Pharmacokinetic Assessments	Added the following: For consented patients during unsual circumstances, e.g. global pandemics, and unable to provide samples these will not be protocol deviations.

Summary of Changes: eXALT3: Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

Amendment #: 5.0 (COVID-19)
Amendment Date: 11May2020

	Revision(s) Made
9.8 Pharmacogenetic Assessment	For consented patients during unsual circumstances, e.g. global pandemics, and unable to provide samples these will not be protocol deviations.
9.9 Biomarkers	For consented patients during unsual circumstances, e.g global pandemics, and unable to provide samples these will not be protocol deviations.
9.9.2 Biomarker Blood Samples for ALK and Treatment Response Testing	Deleted the lined out and added the bold to the following: During treatment, optional biomarker blood samples will be taken for exploratory evaluation of nucleic acids (such as DNA, RNA) and/or proteins at the ~~following~~ **below** time points. **For consented patients during unsual circumstances, e.g. global pandemics, and unable to provide samples these will not be protocol deviations.**
10.1 Labeling, Packaging, and Supply	Deleted the lined out and added the bold to the following: Upon randomization to the ensartinib arm, the clinical site pharmacist will **initially** dispense **225mg of ensartinib, then appropriate amount during subsequent visits.**~~two bottles 30 ct 100 mg and 1 bottle of 30 ct 25 mg of ensartinib. The~~ **An** appropriate **number of 30 capsule containers should be dispensed** ~~bottles of 30 capsules each should be sufficient~~ for the patient's treatment until the next visit (and potential overage to maintain their dosing routine). Any unused study drug must be returned to the site. **If there is concern about risk of exposure to COVID-19, home delivery of investigational product that would not raise any new safety risks may be implemented to protect patients from coming to clinical trial sites. In all cases, requirements under FDA regulations for maintaining required investigational product storage conditions and investigational product accountability remain.** **Note that crizotinib will be supplied** by the Sponsor. Crizotinib will be supplied in either cartons or bottles depending on it's manufacturing location.
12. Study Drug	Deleted the lined out and added the bold to the following: Study drug will be selfadministered by the patient. The investigator or authorized designee will provide verbal dosing instructions prior to dispensing~~. medications at each of the specified visits~~ and appropriate instructions incorporated on the bottle label. This discussion should be documented in the source documents. **During unsual circumstances, e.g. global pandemics, alternative formats for instructions (phone calls, emails, etc.) may be used, but also documented.**

Summary of Changes: eXALT3: Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

Amendment #: 5.0 (COVID-19)

~~Amendment Date: 11May2020~~	~~**Revision(s) Made**~~
15.3 Analysis Populations	Added the following sentence: Additional sensitivity analyses will be conducted to assess the impact of the global pandemic on potential missing data.
15.7.1 Primary Analysis	Added the bolded to the following sentence: Additonal sensitivity analyses **such as** Efficacy **global pandemic impact on potential missing data** may be specified in the SAP.
15.7.2 Secondary/Exploratory Efficacy Analysis	Added the bolded to the following sentence: First interim analysis will be performed when a total of 56 deaths are expected at **approximately** 75% (143/190) of maturity for PFS events by IRR.
15.7.2 Secondary/Exploratory Efficacy Analysis	Moved the following from Exploratory efficacy endpoints to Other secondary efficacy endpoints: Patient reported time to deterioration (TTD) as measured by the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale Patient reported health-related quality of life (HRQoL) as measured by the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale
Section 15.10.5 Power and Sample Size Determination	Added the bolded to the following sentence: An interim analysis will be performed after approximately 75% of the planned PFS events per IRR have occurred (**approximately** 143 of 190 total events).
17 Early Termination of Study	Added the bolded to the following sentence: The study may be terminated at any time by the Sponsor, such as in the event of unacceptable toxicity or new information that significantly impacts patient safety **or the impossibility to guarantee study conduct per protocol or patients' safety in case of unforeseen circumstances (i.e. a pandemic as the COVID-19)**.

Summary of Changes: eXALT3: Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

Amendment #: 5.0 (COVID-19)

~~Amendment Date: 11May2020~~	~~**Revision(s) Made**~~
19.4 Informed Consent	Added the following: During unsual circumstances, e.g. global pandemics, alternative processes to consent may be used, for example, the consent form may be sent to the subject or the subject's legally authorized representative by facsimile or e-mail, and the consent interview may then be conducted by telephone when the subject or subject's legally authorized representative can read the consent form during the discussion. There may be other adequate alternatives, however, the patient should also be reconcented once able to visit the investigative site. Alternate consenting processes, should be approved by overseeing ethics committees.
20.5 Trial Monitoring, Auditing, and Inspecting	Added the following sentence: During unsual circumstances, e.g. global pandemics, alternatives to onsite source document verification or data reviews may be used if local regulations/ethics committees allow, such as remote monitoring.,
Appendix E Schedule of Assessments for Protocol X396CLI-301	In superscript x, deleted the lined out text in the following: a.Follow-up for survival should be obtained in all patients after completion of study treatment. This should be done approximately ~~every 3 months for the first year after the end of treatment and then approximately~~ every 6 months. Note: patients that end treatment for reasons other than disease progression should continue to be followed every 8 weeks (see section 9.6.4.1). Once disease progression occurs per RECIST criteria, then follow for survival approximately ~~every 3 months for the first year and then approximately every~~ 6 months."
Appendix E Schedule of Assessments for Protocol X396CLI-301	Updated "Cycle 19 Through End of Treatment" column for increased frequency (12 weeks). Also, adjusted the appropriate superscript texts (h, m, n, q). Added superscript y.

CLINICAL PROTOCOL X396-CLI-301 SYNOPSIS

Title of Trial:	Phase 3, Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients	
Protocol Number:	X396-CLI-301	
Sponsor:	Xcovery Holdings Inc	
Trial Duration:	The expected duration of the study is approximately 48 months.	**Phase of Trial:** 3
Trial Centers:	This study may include up to 170 sites worldwide.	
Objectives:	**Primary:** • To evaluate the efficacy and safety of ensartinib vs. crizotinib in patients with ALK-positive NSCLC that have received up to 1 prior chemotherapy regimen and no prior ALK tyrosine kinase inhibitor (TKI). **Secondary:** • To obtain additional pharmacokinetic (PK) data on ensartinib from sparse PK sampling from patients at selected sites. • To compare the quality of life (QoL) in patients receiving ensartinib vs. crizotinib. • **Exploratory:** • To evaluate the status of exploratory biomarkers and correlate with clinical outcome. • To obtain germline DNA samples for possible pharmacogenetic analysis in the event that outliers with respect to efficacy, tolerability/safety, or exposure are	
Efficacy Endpoints:	**Primary:** • Progression-free survival (PFS) as assessed by independent radiology review (IRR) based on RECIST v. 1.1 criteria. **Secondary:** • Key Secondary Efficacy Endpoints: Overall survival, CNS response rate (based on IRR), time to CNS progression (based on IRR), objective response rate (based on IRR) • Other Secondary Efficacy Endpoints: PFS (based on investigator assessment), ORR (based on investigator assessment), time to response (based on investigator assessment and IRR), duration of response (based on investigator assessment and IRR), CNS response rate (based on investigator assessment), time to CNS progression (based on investigator assessment). Patient reported time to deterioration (TTD) as measured by the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale (LCSS), patient reported health-related quality of life (HRQoL) as measured by the EORTC C30/LC13 QoL questionnaire and LCSS, **Exploratory:** • pharmacodynamic (PD) and possible pharmacogenetic (PG) assessments and biomarkers in blood or/and tissue sample. Biomarkers in the blood or tissue related to efficacy.	

CLINICAL PROTOCOL X396-CLI-301 SYNOPSIS (continued)

Trial Design:	A Phase 3 open-label, randomized study of the ALK inhibitors ensartinib and crizotinib given as single agents
Trial Population:	This study will be conducted in patients ≥18 years of age with ALK+ NSCLC.
Number of Patients:	Up to 316 patients are planned to be enrolled in this study.
Trial Drug, Dose, and Mode of Administration:	Ensartinib 225 mg will be given orally once daily (QD) or crizotinib 250 mg will be given orally twice daily (BID), each on a 28 day schedule.
Inclusion Criteria:	6. Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK-positive by an FDA-approved assay performed centrally. Patients must be ALK positive by local test prior to submitting tissue to the central lab. Randomization will occur after ALK positive confirmation is received from the central lab. Patients may have received up to 1 prior chemotherapy regimen for metastatic disease, which may also include maintenance therapy. Note that patients that have received adjuvant or neoadjuvant chemotherapy and developed metastatic disease within 6 months from the end of that therapy would be considered to have received 1 prior regimen for metastatic disease. 7. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 to 2. (see Appendix A) 8. Life expectancy of at least 12 weeks. 9. Ability to swallow and retain oral medication. 5. Adequate organ system function, defined as follows: a Absolute neutrophil count (ANC) ≥1.5 x 10^9/L b Platelets ≥100 x 10^9/L c Hemoglobin ≥9 g/dL (≥90 g/L) Note that transfusions are allowed to meet the required hemoglobin level d Total bilirubin ≤1.5 times the upper limit of normal (ULN) e Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x ULN with liver involvement. f Creatinine ≤1.5 x ULN. If >1.5 x ULN, patient may still be eligible if calculated creatinine clearance ≥50 mL/min (0.83 mL/s) as calculated by the Cockcroft-Gault method. 10. Brain metastases allowed if asymptomatic at study baseline. Patients with untreated brain metastases must not be on corticosteroids. If patients have neurological symptoms or signs due to CNS metastases, patients need to complete whole brain radiation or focal treatment at least 14 days before start of study treatment and be asymptomatic on stable or decreasing doses of corticosteroids at baseline. 11. Men with partners of childbearing potential willing to use adequate contraceptive measures during the study and for 90 days after the last dose of study medication. 12. Women who are not of child-bearing potential, and women of child-bearing potential who agree to use adequate contraceptive measures during the study and for 90 days after the last dose of study medication, and

	who have a negative serum or urine pregnancy test within 1 week prior to initial trial treatment. 13. Patients must be ≥18 years of age. 14. Patients must have measurable disease per RECIST v. 1.1. 15. Willingness and ability to comply with the trial and follow-up procedures. 16. Ability to understand the nature of this trial and give written informed consent. Note the following pertains to patients enrolled in France 17. In France, a subject will be eligible for inclusion in this study only affiliated to the French Social Security system, and currently benefit from the corresponding rights and cover.
Exclusion Criteria:	1. Patients that have previously received an ALK TKI or PD-1/PD-L1 therapy, and patients currently receiving cancer therapy (i.e., other targeted therapies, chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization). 2. Use of an investigational drug within 21 days prior to the first dose of study drug. Note that to be eligible, any drug-related toxicity should have recovered to Grade 1 or less, with the exception of alopecia. 3. Any chemotherapy within 4 weeks, or major surgery or radiotherapy within the last 14 days 4. Patients with primary CNS tumors and leptomeningeal disease are ineligible. 5. Patients with a previous malignancy within the past 3 years (other than curatively treated basal cell carcinoma of the skin, in situ carcinoma of the cervix, or any cancer that is considered to be cured and have no impact on PFS and OS for the current NSCLC) 6. Concomitant systemic use of anticancer herbal medications. These should be stopped prior to study entry. 7. Patients receiving a. strong CYP3A inhibitors (including, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, grapefruit, grapefruit juice) b. strong CYP3A inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's Wort) c. CYP3A substrates with narrow therapeutic window (including, but not limited to, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus). 8. Women who are pregnant or breastfeeding. 9. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of study medications 10. Patients at risk for GI perforation. 11. Clinically significant cardiovascular disease including: a. QTcF interval >450 ms for men and >470 ms for women, symptomatic bradycardia <45 beats per minute or other significant ECG abnormalities in the investigator's opinion. b. Clinically uncontrolled hypertension in the investigator's opinion (e.g., blood pressure >160/100 mmHg; note that isolated elevated readings considered to not be indicative of uncontrolled hypertension are allowed). The following within 6 months prior to Cycle 1 Day 1:

	14. Congestive heart failure (New York Heart Class III or IV). b. Arrhythmia or conduction abnormality requiring medication. Note: patients with atrial fibrillation/flutter controlled by medication and arrhythmias controlled by pacemakers are eligible. c. Severe/unstable angina, coronary artery/peripheral bypass graft, or myocardial infarction. d. Cerebrovascular accident or transient ischemia 12. Patients who are immunosuppressed (including known HIV infection), have a serious active infection at the time of treatment, have interstitial lung disease/pneumonitis, or have any serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. Patients with controlled hepatitis C, in the investigator's opinion, are allowed. Patients with known hepatitis B must be HBeAg and HB viral DNA negative for enrollment. Note that, because of the high prevalence, all patients in the Asia-Pacific region (except Australia, New Zealand, and Japan) must be tested and, if HBsAg positive, must be HBeAg and HB viral DNA negative for enrollment 13. Known hypersensitivity to tartrazine, a dye used in the ensartinib 100 mg capsule. 14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol. 15. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol or would impart excessive risk associated with study participation that would make it inappropriate for the patient to be enrolled. 16. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol. Note the following pertains to patients enrolled in France 17. In France, a subject will not be eligible when under legal protection.

Statistical Methodology:	This is an open-label, randomized, Phase 3 study comparing the efficacy and safety of the ALK inhibitors ensartinib and crizotinib in patients with ALK+ NSCLC. The primary efficacy endpoint will be PFS based upon an independent radiology review. **Power and Sample Size Determination:** This study will enroll up to 316 intent-to-treat (ITT) patients using a 1:1 randomization. A sample size of 266 will allow detection of a hazard ratio of 0.625, with 90% power and a 2-sided alpha of 0.05 in the ITT population. This estimate assumes a median PFS of 10 months in the crizotinib arm (based on the assumption that approximately 2/3 of patients will be chemotherapy-naïve), with an improvement to 16 months in the ensartinib arm, and 27 month accrual period with 12 months of additional follow-up. The final analysis will be performed after 190 PFS events have been observed in the ITT population. An interim analysis will be performed after approximately 75% of the planned PFS events per IRR have occurred (around 143 of 190 total events) in ITT population. **Statistical Methods:** The primary efficacy endpoint will be PFS based upon an independent radiology review. The primary analysis will be based on the ITT population. PFS will be tested using a log-rank test and the median will be estimated for each treatment arm using the Kaplan-Meier method. Hazard ratio will be estimated using the Cox regression model. The overall 2-sided Type I error rate will be controlled at 0.05. One interim analysis is planned after approximately 75% of the total expected PFS events have been observed in the ITT population. An O'Brien-Fleming Lan-DeMets (DeMets and Lan, 1994) alpha spending function will be use to control at 2-sided alpha of 0.05. The interim analysis will be performed after approximately the first 143 events have been observed and the primary endpoint of PFS will be tested at a 2-sided alpha level of 0.019. Among key secondary endpoints, only OS will be tested formally at 0.05 if the primary endpoints of PFS is statistically significant. Further details on the statistical analyses will be provided in the Statistical Analysis Plan (SAP).

Correlative Testing:	Tumor tissue and optional blood samples will be collected and may be analyzed for exploratory biomarkers to assess correlation with clinical outcomes from study participants. In addition, blood samples will be obtained from as many ensartinib patients as possible for possible pharmacogenetic analysis. Informed consent must be obtained from any patient who agrees to provide samples for correlative testing.

CLINICAL TRIAL X396-CLI-301 CONTACT INFORMATION:

Sponsor Contact Information:	Xcovery Holdings, Inc 11780 US Highway 1 Suite 202 Palm Beach Gardens, FL 33408 (561) 835-9356
CRO Contact Information:	
Global Medical Monitor:	
Safety Dept. Phone # / Fax # / E-mail Address:	Phone: U.S.: 1-866-758-2798 Worldwide: 1-919-313-7111 Fax: U.S.: 1-866-761-1274 Worldwide: 1-919-313-1412 Email: safety-inbox.biotech@iqvia.com

List of Abbreviations

ABL	Abelson leukemia virus
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALT (SGPT)	alanine aminotransferase
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST (SGOT)	aspartate aminotransferase
AUC	area under the plasma-concentration time curve
AUC_{0-t}	area under the plasma-concentration time curve from zero up to the last measureable concentration
AUC_{0-24}	area under the plasma-concentration time curve from time zero to 24 hours
BID	twice daily
BPM	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood cell count
CDA	ity disclosure agreement
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
C-Kit	CD117 cytokine receptor
C_{max}	peak drug concentration
CNS	central nervous system
CR	complete response
CRO	contract research organization
CT	computerized tomography
CTA	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EPHA2	ephrin A2 kinase
ERT	eResearch Technology, Inc.
ESMO	European Society of Medical Oncology
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded

List of Abbreviations (continued)

FIH	first in human
FISH	fluorescence *in situ* hybridization
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GMP	Good Manufacturing Practice
H&E	hematoxylin and eosin
HB	hepatitis B
HBeAg	hepatitis B e-antigen
HBsAg	hepatitis B surface antigen
HCl	hydrochloride salt
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	health-related
HTN	hypertension
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IMT	inflammatory myofibroblastic tumor
IND	Investigational New Drug
IRB	Institutional Review Board
IRR	Independent Radiology Review
ITT	intent-to-treat
IVRS	interactive voice response system
LCSS	Lung Cancer Symptom Scale
LD	longest diameter
LTK	leukocyte tyrosine kinase
mg	milligram
mg/kg	milligram/kilogram
mg/m^2	milligram/meter squared
ms	millisecond
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	myocardial infarction
mITT	modified intent-to-treat
MTD	maximum tolerated dose
NA	not applicable
NCI	National Cancer Institute
ND	not done
NGS	next generation sequencing
NOAEL	no observed adverse effect level
NOS	not otherwise specified
NPM	nucleophosmin
NSCLC	non-small cell lung cancer

List of Abbreviations (continued)

NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PG	pharmacogenetic
PHI	protected health information
PI	principal investigator
PK	pharmacokinetics
PP	per protocol
PR	partial response
PS	performance status
QA	quality assurance
QD	once daily
QOL	quality of life
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia method
RET	RET oncogene "Rearranged during transfection"
ROS1	transforming gene of avian sarcoma virus UR2
RTK	receptor tyrosine kinases
RT-PCR	reverse transcription polymerase chain reaction
SAD	short axis dimension
SAP	statistical analysis plan
SAR	serious adverse reaction
SAE	serious adverse event
SD	stable disease or standard deviation
SDV	source document verification
SLK	Ste20-like kinase
SOC	system organ class
SOP	standard operating procedure
SRS	stereotactic radiosurgery
STD_{10}	severely toxic dose in 10% of animals
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTD	time to deterioration
TTP	time to tumor progression
ULN	upper limit of normal
U.S.	United States

Table of Contents

List of Appendices

1. INTRODUCTION

1.1. Background

The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that is aberrant in a variety of malignancies. ALK was originally discovered in anaplastic large cell lymphoma (ALCL) as part of a chromosomal translocation t(2,5), which fuses the C-terminal kinase domain of ALK encoded on chromosome 2p23 to the N-terminus of nucleophosmin (NPM) on chromosome 5q35 (Morris et al. 1994). Subsequently, a variety of ALK fusion proteins have been found in multiple malignancies, including inflammatory myofibroblastic tumor (IMT) (Lawrence et al. 2000) and non-small cell lung cancer (NSCLC) (Soda et al. 2007; Choi et al. 2008; Koivunen et al. 2008; Takeuchi et al. 2008; Takeuchi et al. 2009; Wong et al. 2009; Horn and Pao 2009; Rikova et al. 2007). All ALK fusions tested biologically to date have demonstrated gain of function properties (Morris et al. 1994; Soda et al. 2007; Koivunen et al. 2008; Takeuchi et al. 2009). Activating mutations in wild-type ALK have also been identified in both familial and sporadic neuroblastoma. Most of these activating mutations occur within the tyrosine kinase domain and are transforming in vitro and in vivo (Mosse et al. 2008; George et al 2008; Janoueix-Leorosey et al. 2008; Chen et al 2008). Importantly, the activity of cancer-specific ALK variants is required for tumor maintenance. Thus, ALK mutants can serve as 'Achilles heels' to be exploited therapeutically. Multiple preclinical studies have shown that specific small molecule ALK tyrosine kinase inhibitors (TKIs) can delay tumor growth and/or induce tumor regression in xenograft and transgenic models (Soda et al. 2007; Choi et al. 2008; Koivunen et al. 2008; Sabbatini et al. 2009).

Based on such promising nonclinical studies, ALK TKIs entered into clinical trials. The first agent in humans was crizotinib (Xalkori®, Pfizer, also known as PF-2341066 or PF-1066), an orally available small molecule ATP-mimetic compound that was approved for commercial use in the U.S. in August 2011 for the treatment of metastatic NSCLC that is ALK-positive. Crizotinib was originally designed as a MET inhibitor but was recognized to have 'off-target' anti-ALK activity (Zou et al. 2007). Strikingly, in a Phase 1 study, patients with ALK fusionpositive NSCLC demonstrated a >60% radiographic response rate (Bang et al 2008). Crizotinib has been shown to be superior to chemotherapy in the first and second line treatment of patients with ALK fusion-positive NSCLC. By contrast, chemotherapy response rates are <10% in previously treated patients with unselected NSCLC (Hanna et al. 2004). Several other ALK TKIs have entered into clinical trials, with ceritinib (Zykadia®) and alectinib (Alecensa®) being approved in the U.S. for use in patients that have progressed on or are intolerant to crizotinib.

1.1.1. Ensartinib

Xcovery Holdings Inc (the Sponsor) has developed ensartinib, a novel potent and specific ALK inhibitor with potential therapeutic relevance. In *in vitro* and *in vivo* nonclinical studies, ensartinib exhibited a favorable effectiveness profile, including anti-tumor activity against multiple ALK variants including some that are resistant or become resistant to crizotinib.

1.1.1.1. Toxicology

To assess the safety of ensartinib, toxicity studies were conducted in rats and dogs, including pivotal 28-day toxicity studies, 13-week GLP toxicity studies, and a GLP Respiratory Safety Pharmacology Evaluation, a Central Nervous System Safety Pharmacology Evaluation and a Cardiovascular Safety Study. In these studies, ensartinib was administered orally. The 28-day repeat-dose study in rats evaluated doses of 50, 100, and 150 mg/kg/day. At 50 mg/kg/day, minor clinical signs (effects on the skin) were noted, along with a low incidence and severity of acanthosis/hyperkeratosis and squamous cell hyperplasia in the skin and hyperkeratosis in the stomach. More pronounced changes were noted at 100 mg/kg/day and included skin lesions, decreased body weight and food consumption, changes in hematology parameters, and the same type of microscopic changes in the skin and stomach as were observed at the low dose. Administration of ensartinib resulted in mortality or moribund sacrifice at 150 mg/kg/day and significant adverse effects on the skin, significant decreases in body weight, weight gain and food consumption, more pronounced hematology changes, and the same microscopic findings as occurred at 50 mg/kg/day but at a higher incidence and severity. After a 2-week recovery phase, the test article-related changes were reversed or decreased in severity compared with the dosing phase. Based on these data, 50 mg/kg/day (300 mg/m^2) was considered to be the dose producing severe toxicity to 10% of the animals (STD_{10}).

In the 28-day study in dogs, doses of 15, 30/22.5, and 60 mg/kg/day were evaluated. Beginning on Days 12 and 22, the mid-dose was decreased to 22.5 mg/kg/day in the females and males, respectively, due to toxicity. This decrease occurred after a 3-day drug holiday in both genders. At 15 mg/kg/day, effects included skin lesions, emesis or vomitus, decreased thymus weight, and microscopic changes in the skin (i.e., acanthosis/hyperkeratosis, chronic-active inflammation, squamous cell hyperplasia, and/or ulcer [males only]). The mid-dose of 30 mg/kg/day produced adverse clinical signs that required a drug holiday and a decrease in the dose to 22.5 mg/kg/day. Other findings were similar to those noted at 15 mg/kg/day, but decreased food consumption and lymphocyte depletion of the spleen and thymus also occurred. Finally, pronounced adverse effects (e.g., clinical signs, weight loss, and clinical pathology changes) were reported at 60 mg/kg/day. The animals in this group were terminated after 5 days of dosing. Some evidence of recovery was observed in the females; this could not be assessed in the males as they were sacrificed due to poor condition on the second day of recovery. The highest non-severely toxic dose (HNSTD) was determined to be 15 mg/kg/day (300 mg/m^2), given that the changes did not affect the normal physiological functioning of the dogs and were not life-threatening.

In the 13-week GLP toxicology study followed by a 4 week recovery phase, once daily administration of 12.5, 25 or 50 mg/kg/day X-396 via oral gavage to rats were relatively well tolerated. X-396-related findings included scabs and thinning of the hair coat, which was predominantly in males given 50 mg/kg/day and correlated with hyperkeratosis and mixed cell inflammation of the skin. The skin lesions did not affect the overall well-being of the animal and indicated reversal during the recovery phase. Based on these findings, the no observable adverse effect level (NOAEL) for X-396 is 50 mg/kg/day.

In the 13-week GLP toxicology study followed by a 4 week recovery phase, once daily administration of 5, 10, or 20/15 mg/kg/day X-396 via oral gavage to dogs resulted in adverse skin and pelage lesions that required veterinary intervention and dose suspension for six days,

followed by dose reduction to 15 mg/kg/day. The adverse clinical observations for skin lesions of animals given 20 mg/kg/day correlated with clinical and anatomic pathology findings. The findings were less severe and showed reversal after the dose was reduced to 15 mg/kg/day, followed by a 4-week recovery. Based on these findings, the no observed adverse effect level (NOAEL) for X-396 is 15 mg/kg/day.

There was no indication that ensartinib adversely affected the core organ systems (i.e., cardiovascular, respiratory, central nervous systems) in the repeat-dose toxicology studies or the Safety Pharmacology studies. Evaluation of the clinical signs data and electrocardiograms (collected in dogs) did not reveal an indication of adverse effects on the three core organ systems.

Refer to the Ensartinib Investigator's Brochure (IB) for detailed information regarding the toxicology studies conducted to date.

1.1.1.2. Pharmacokinetics

Following single oral doses, absorption was generally rapid for rats and dogs. The data for both species indicated dose-dependent increases in C_{max} and AUC_{0-24}, variable gender effects, and modest accumulation with repeated dosing.

Ensartinib exhibited tumor levels in mice that were 2 to 6 times plasma concentrations at 2 or 4 hrs. Brain concentrations were approximately 13% of plasma concentrations at the same time, indicating preferential distribution to the tumor relative to plasma or brain.

Ensartinib was extensively protein bound in mice, rats, dogs, or humans (values ranging from 90.2% to 97%), with no apparent concentration dependence. Incubation with liver microsomes from dogs, monkeys, and humans revealed 20 potential metabolites; M14 was the most prominent metabolite for all three species. Based on metabolite patterns, it was concluded that the dog is an appropriate non-rodent species for toxicology studies.

Ensartinib did not did not inhibit the cytochrome P450 isozymes CYP 1A2 or 2D6, but did inhibit 3A4 by 22% and 2C9 by 43% at 10 μM. However, at 225 mg QD, the highest observed Cmax in NSCLC patients is 1.1 μM with the average being approximately 442 nM (fasted) and 735 nM (fed), suggesting that significant CYP 3A4 or 2C9 inhibition by ensartinib in the clinic is unlikely.

Refer to the Ensartinib IB for detailed information regarding the PK studies conducted to date.

1.1.1.3. Pharmacology/Pharmacodynamic Studies

Ensartinib was 10-fold more potent than crizotinib in *in vitro* kinase binding assays and in inhibiting autophosphorylation of ALK in cells (Lovly et al. 2011). *In vitro* cell proliferation assays showed that the anti-proliferative activity of ensartinib was selective for cells with deregulated ALK. The anti-proliferative activity was about 10-fold the potency of crizotinib in NSCLC, lymphoma and neuroblastoma lines with deregulated ALK. Several mutations (F1174L, L1196M, and C1156Y) that confer resistance to crizotinib in the clinic were potently inhibited by ensartinib with IC_{50}s in cell proliferation assays near 100 nM or less. The effect on mutant cells was again about 10-fold more potent than crizotinib and suggests that X-396 may be effective in mutant cells resistant to crizotinib (Lovly et al. 2011).

Ensartinibwas also a potent inhibitor of MET, and it exhibited an IC_{50} of <25 nM in six additional kinases in an *in vitro* kinase catalytic assay: ABL T315I (gatekeeper mutation of Abelson leukemia virus), Axl, EPHA2 (Ephrin A2 kinase), LTK (leukocyte tyrosine kinase), ROS1 (transforming gene of avian sarcoma virus UR2) and SLK (Ste20-like kinase). Several of these kinases have been implicated in tumorigenesis of both leukemias and multiple solid tumor types (O'Bryan et al. 1991; Yap et al. 2010; Tandon et al. 2011; Acquaviva et al. 2008). In particular, both MET and EPHA2 have been reported to be deregulated broadly across multiple solid tumor types and, as such, these activities could contribute to anti-tumor activity observed with X-396 (Yap et al. 2010; Tandon et al. 2011).

In animal studies, ensartinib induced tumor stasis at well tolerated doses in xenografts of human EML4-ALK positive NSCLC in nude mice. Human tumor xenografts of the neuroblastoma SH-SY5Y that carries a crizotinib-resistant mutation (F1174L) were growth inhibited byensartinib. These same cells were adapted to an intracranial model and treated with ensartinib and crizotinib at equivalent doses. A significant increase in life span was observed in mice treated with ensartinib but not in mice treated with crizotinib in this brain penetration model. These data support the potential utility of ensartinibin crizotinib-resistant tumors and support the potential use of ensartinib for the treatment of NSCLC tumors that have metastasized to the brain.

Refer to the ensartinib IB for detailed information regarding the pharmacodynamic (PD) studies conducted to date.

1.1.1.4. Clinical Studies

As of December 2016, a total of 89 patients had been treated in the Phase 1/2, first-in-human (FIH) study with 36 in the dose escalation portion and 53 patients in the expansion cohort phase. Doses ranged from 25 mg to 250 mg once daily (QD). During the dose escalation phase of the study, ensartinib was generally well-tolerated. Only 2 patients developed dose-limiting toxicities (DLTs; fluid overload and rash) and the maximum tolerated dose (MTD) was not officially reached. However, a dose of 225 mg QD was selected as the dose to evaluate further in the expansion cohort phase of the study and subsequent studies because of Grade 3 rash observed in patients at the 250 mg dose level. Dosing was initially done with patients fasting, but the last cohort evaluated the drug when given with food. Preliminary data suggests that there is little difference in exposure based on whether the drug is taken with or without food but less GI toxicity was observed when taken with food.

The most common drug-related side effects are rash (55%), nausea (37%), vomiting (27%), and fatigue (21%); the majority of those were grade 1-2. The safety profile of ensartinib appears to be different from that of the other ALK TKIs, with rash being the most prominent side effect. However, the rash is easily managed. Ensartinib appears to be well-tolerated with respect to GI toxicities, particularly diarrhea, and liver toxicity.

With respect to efficacy, the preliminary data suggest that the ORR, duration of response, and PFS are similar to those of other ALK TKIs. 13 of 15 ALK TKI naïve patients responded to ensartinib (the two patients who did not respond were FISH positive but plasma NGS negative).

The median PFS is immature since only three of the 13 responders progressed after 9.5, 23.9, and 26.5 months. In patients who were resistant to crizotinib, the objective response rate was 70%

with median PFS of 9.2 months. 8 of 13 patients with CNS target lesion(s) had objective responses and the other five had stable disease.

1.1.1.5. Ensartinib Overall Risk-Assessment

The current risk profile for ensartinib is based on safety data collected from completed nonclinical studies and ongoing trials with ensartinib, as well as labeling for similar products, crizotinib (Xalkori®), ceritinib (Zykadia®), alectinib (Alecensa®), and brigatinib (Alunbrig®).

From the ensartinib toxicology studies in rats and dogs, the most common clinical findings involved the skin and included red discoloration, scabs, and sores. Alopecia was observed in rats. One dog developed a squamous cell papilloma; the pathologist determined the relationship of ensartinib treatment to an isolated papilloma not seen in any other animal even at higher drug doses was uncertain. Vomiting was observed in dogs, and weight loss was observed in both species. Pathology findings included skin changes (e.g., acanthosis/hyperkeratosis, inflammation, squamous cell hyperplasia, and ulcers), stomach changes in the rat (hyperkeratosis), and hypocellularity of the bone marrow and lymphoid depletion of the spleen and thymus. Laboratory findings were generally mild to moderate, and many of the findings, particularly in the dog, were observed only at the highest dose studied. Laboratory findings included decreased red blood cell counts, increased and decreased reticulocyte counts, decreased platelet counts, decreased white blood cell and lymphocyte counts, increased and decreased neutrophil and monocyte counts, decreased protein, albumin, and calcium (the latter thought to be related to the decreased albumin), increased liver tests (e.g., aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, and bilirubin, although there was no microscopic evidence of liver injury), and increased creatine kinase (although there was no microscopic evidence of muscle injury). There were no ophthalmologic or electrocardiographic effects noted. A phototoxicity study was not performed.

To date, the most common drug-related AEs (≥10% of patients) observed with ensartinib from the Phase I/II study include rash (various descriptions, including rash, erythema/erythematous rash, macular rash, maculopapular rash, acneiform rash, pruritic rash, pustular rash, follicular rash, skin exfoliation, eczema, lichenoid keratosis/dermatitis, and photosensitivity), nausea, vomiting, fatigue, edema (including peripheral edema, facial edema, periorbital edema), pruritus, dry skin, decreased appetite, diarrhea, aspartate aminotransferase increased, alanine aminotransferase increased, and constipation. Serious AEs from the Phase I/II and the Phase III studies considered drug-related by the investigator include the following:

- Grade 4 thrombotic microangiopathy (including increased serum creatinine, proteinuria, decreased platelets, worsening anemia, hypertension), ultimately requiring hemodialysis. [The investigator considered the event to be an idiosyncratic reaction possibly related to study drug, but while it is not possible to rule out a relationship to study drug, the Sponsor's overall assessment is that the event was unlikely to be related to study drug and was more likely related to other factors].
- Grade 2 elevation of ALT

- Grade 3 elevation of bilirubin. However, the bilirubin remained elevated 2 months after discontinuing drug and, with other risk factors, the Sponsor considers the event to be unlikely related to study drug
- Grade 2 peripheral edema and fluid overload (resulting in fatigue, shortness of breath on exertion, localized lower extremity edema, weight gain)
- Grade 3 erythematous rash of the face and body, with itching (2); one was also accompanied by dry, peeling skin
- Grade 3 pneumonitis
- Grade 3 dehydration (2), one with a grade 3 UTI. However, it is unclear that these were related to study drug.

Patients described above experiencing thrombotic microangiopathy, elevated ALT and bilirubin, and pneumonitis were discontinued from the study; all others were able to tolerate a regimen where the dose was held and/or continued or reduced.

Separately, under Investigator IND #132491, an occurrence of pericardial effusion was deemed possibly drug-related by the investigator. The Sponsor did not consider this event drug-related, but rather related to the patient's underlying malignancy.

Under Investigator IND #131960, there was a report of an allergic reaction (Grade 3) considered by the investigator to be probably drug-related. There were some indications of a pre-existing condition, but the Sponsor considers the event to be possibly related at this time.

Note: Ensartinib 100 mg capsules contain FD+C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD+C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Crizotinib was approved in the U.S. in August 2011 for the treatment of patients with locally advanced or metastatic NSCLC that is ALK-positive. Ceritinib was approved in the U.S. in April 2014 for the treatment of patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib. Alectinib was approved in the U.S. in December 2015 and brigatinib in April 2017 for the treatment of patients with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib. From the labeling for one or more of these agents, Warnings and Precautions include interstitial lung disease/pneumonitis, hepatotoxicity, QT interval prolongation, bradycardia, hypertension, severe or persistent gastrointestinal toxicity, hyperglycemia, severe myalgia and creatine phosphokinase elevation, severe visual loss/visual disturbance, pancreatitis/pancreatic enzyme elevation, renal impairment, and embryofetal toxicity. Common adverse reactions (≥10%) in clinical trials noted in the labeling for one or more of these agents include visual disorders (e.g., diplopia, photopsia, photophobia, blurred vision, visual impairment, vitreous floaters, eye strain, vitreous detachment, macular edema, visual field defect, and reduced visual acuity), nausea, vomiting, diarrhea, constipation, esophageal disorder (including dyspepsia, gastroesophageal reflux, dysphagia), abdominal pain, edema, fatigue, bradycardia, prolonged QT interval, hypertension, upper respiratory infection, pneumonia, fever, cough, dyspnea, elevated transaminases, decreased appetite, weight decreased or increased, myalgia, muscle spasms, musculoskeletal pain, non-cardiac chest pain, back pain, arthralgia, pain in extremity, dizziness/balance disorder, headache, insomnia, neuropathy,

dysgeusia, renal impairmen, and rash (XALKORI® (crizotinib) PI 2017; ZYKADIA® (ceritinib) PI 2017, ALECENSA® (alectinib) PI 2017, ALUNBRIG® (brigatinib) PI 2017. In addition, photosensitivity precautions are suggested for at least one of these agents, and there has been a report of decreased testosterone in patients receiving crizotinib (Weickhardt et al. 2012). The extent to which adverse events associated with related compounds or the non-clinical toxicology findings noted with ensartinib will be observed in the clinical trials is unknown.

1.1.2. Crizotinib

For additional information about crizotinib, please refer to the Xalkori® (crizotinib) prescribing information.

1.2. Rationale

1.2.1. Rationale for the Trial

ALK rearrangements are reported in approximately 2-7% of patients with NSCLC (Kwak et al. 2010). Crizotinib was the first ALK inhibitor to enter clinical trials and to be approved by the FDA. It was approved in August 2011 for the treatment of ALK-positive patients with NSCLC. Patients receiving crizotinib have a high response rate (65%) in patients previously treated with one platinum-containing regimen (Xalkori® PI 2014). However, patients relapse, often in the CNS. The median duration of response with crizotinib (in the patients that had previously received one platinum-containing regimen) is 7.7 months (Xalkori® PI 2014), and in patients without prior chemotherapy, median PFS was 10.9 months (Mok et al. 2014). Secondgeneration ALK inhibitors are in clinical trials, with ceritinib (LDK378) and alectinib having received accelerated approval in April 2014 and December 2015, respectively, for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. Phase 3 studies with ceritinib and alectinib are ongoing, including in the first- and second-line settings vs. chemotherapy or crizotinib, and after failure of platinum and crizotinib. Other 2nd generation ALK TKIs, such as brigatinib (AP26113) are in development.

Response rates with the various ALK TKIs that have been approved or are in development have generally been similar to date. However, there are differences in sensitivity of some of the ALK mutations to the various ALK TKIs in cell-based assays. In addition, some of the ALK TKIs are better tolerated than others. The safety profile for ensartinib appears to be different than the other ALK TKIs. Based on the safety profile and preliminary efficacy results observed with ensartinib to date, and with ensartinib being approximately 10-fold more potent than crizotinib in enzyme and cell-based assays, Xcovery proposes to evaluate ensartinib in a Phase 3 study vs. crizotinib in the first-line setting. It is anticipated that this will result in a similar or better objective response rate with more durable responses than crizotinib and a longer PFS, and better responses in patients with CNS metastases.

This trial will be conducted in accordance with the International Conference on Harmonisation (ICH) guideline on Good Clinical Practice (GCP) (E6) [ICH/GCP], U.S. Food and Drug

Administration (FDA) Title 21 of the Code of Federal Regulations (CFR) parts 50, 54, 56, and 312, and any other applicable local regulatory requirements.

2. TRIAL OBJECTIVES

2.1. Primary Objectives

The primary objectives of this trial are:

- To evaluate the efficacy and safety of ensartinib vs. crizotinib in patients with ALK-positive NSCLC that have received up to 1 prior chemotherapy regimen and no prior ALK TKI.

2.2. Secondary Objectives

The secondary objectives of this trial are:

- To obtain additional pharmacokinetic (PK) data on ensartinib from sparse PK sampling from patients at selected sites.
- To compare the quality of life (QoL) in patients receiving ensartinib vs. crizotinib.

2.3. Exploratory Objectives

- To evaluate the status of exploratory biomarkers and correlate with clinical outcome.
- To obtain germline DNA samples for possible pharmacogenetic analysis in the event that outliers with respect to efficacy, tolerability/safety, or exposure are identified.

3. STUDY ENDPOINTS

3.1. Primary Efficacy Endpoints

- Progression- free survival (PFS) as assessed by independent radiology review based on RECIST v. 1.1 criteria

3.2. Secondary Efficacy Endpoints

Key Secondary Efficacy Endpoints

- Overall survival
- CNS response rate (based on independent radiology review[IRR])
- Time to CNS progression (based on IRR)
- Objective response rate (ORR; based on IRR)

Other Secondary Efficacy Endpoints

- PFS (based on investigator assessment)

- ORR (based on investigator assessment)
- Time to response (based on investigator assessment and independent radiology review)
- Duration of response (based on investigator assessment and independent radiology review)
- CNS response rate (based on investigator assessment)Time to CNS progression (based on investigator assessment)
- Patient reported time to deterioration (TTD) as measured by the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale (LCSS)

Patient reported health-related quality of life (HRQoL) as measured by the EORTC C30/LC13 QoL questionnaire and LCSS

3.3. Exploratory Endpoints

- Pharmacodynamic (PD) and possible pharmacogenetic (PG) assessments
- Biomarkers in blood and/or tissue samples

4. TRIAL DESIGN

This is a Phase 3, open-label, randomized study of the ALK inhibitors ensartinib and crizotinib given as single agents given to adult patients with ALK-positive NSCLC. Patients will be randomized 1:1. Up to 316 patients are expected to be enrolled in this study at up to 170 sites worldwide.

The study drugs will be given orally daily on a 28-day schedule. Ensartinib 225 mg will be given once daily (QD) or crizotinib 250 mg will be given twice daily (BID).

5. TRIAL POPULATION

5.1. Inclusion Criteria

Patients must meet the following criteria in order to be included in this clinical trial:

1. Histologically or cytologically confirmed diagnosis of advanced or recurrent (Stage IIIB not amenable for multimodality treatment) or metastatic (Stage IV) NSCLC that is ALK-positive by an FDA-approved assay performed centrally. Patients must be ALK positive by local test prior to submitting tissue to the central lab. Randomization will occur after ALK positive confirmation is received from the central lab. Patients may have received up to 1 prior chemotherapy regimen for metastatic disease, which may also include maintenance therapy. Note that patients that have received adjuvant or neoadjuvant chemotherapy and developed metastatic disease within 6 months from the end of that therapy would be considered to have received 1 prior regimen for metastatic disease.
2. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 to 2. (see Appendix A)
3. Life expectancy of at least 12 weeks.

4. Ability to swallow and retain oral medication
5. Adequate organ system function, defined as follows:
   a. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
   b. Platelets ≥100 x 10^9/L
   c. Hemoglobin ≥9 g/dL (≥90 g/L). Note that transfusions are allowed to meet the required hemoglobin level
   d. Total bilirubin ≤1.5 times the upper limit of normal (ULN)
   e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x ULN if no liver involvement or ≤5 x ULN with liver involvement.
   f. Creatinine ≤1.5 x ULN. If >1.5 x ULN, patient may still be eligible if calculated creatinine clearance ≥50 mL/min (0.83 mL/s) as calculated by the Cockcroft-Gault method.
6. Brain metastases allowed if asymptomatic at study baseline. Patients with untreated brain metastases must not be on corticosteroids. If patients have neurological symptoms or signs due to CNS metastases, patients need to complete whole brain radiation or focal treatment at least 14 days before start of study treatment and be asymptomatic on stable or decreasing doses of corticosteroids at baseline.
7. Men with partners of childbearing potential willing to use adequate contraceptive measures during the study and for 90 days after the last dose of study medication.
8. Women who are not of child-bearing potential, and women of child-bearing potential who agree to use adequate contraceptive measures during the study and for 90 days after the last dose of study medication, and who have a negative serum or urine pregnancy test within 1 week prior to initial trial treatment.
9. Patients must be ≥18 years of age.
10. Patients must have measurable disease per RECIST v. 1.1.
11. Willingness and ability to comply with the trial and follow-up procedures.
12. Ability to understand the nature of this trial and give written informed consent.

    Note the following pertains to patients enrolled in France

13. Specific to France: Subjects will be eligible for inclusion in this study only affiliated to the French Social Security system, and currently benefit from the corresponding rights and cover.

5.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from trial entry:

1. Patients that have previously received an ALK TKI or PD-1/PD-L1 therapy, and patients currently receiving cancer therapy (i.e., other targeted therapies, chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery and/or tumor embolization).

2. Use of an investigational drug within 21 days prior to the first dose of study drug. Note that to be eligible, any drug-related toxicity should have recovered to Grade 1 or less, with the exception of alopecia.
3. Any chemotherapy within 4 weeks, or major surgery or radiotherapy within the last 14 days.
4. Patients with primary CNS tumors and leptomeningeal disease are ineligible.
5. Patients with a previous malignancy within the past 3 years (other than curatively treated basal cell carcinoma of the skin, in situ carcinoma of the cervix, or any cancer that is considered to be cured and have no impact on PFS and OS for the current NSCLC).
6. Concomitant systemic use of anticancer herbal medications. These should be stopped prior to study entry.
7. Patients receiving:
    a. Strong CYP3A inhibitors (including, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, grapefruit, grapefruit juice)
    b. Strong CYP3A inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's Wort)
    c. CYP3A substrates with narrow therapeutic window (including, but not limited to, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).
8. Women who are pregnant or breastfeeding.
9. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of study medications.
10. Patients at risk for GI perforation.
11. Clinically significant cardiovascular disease including:
    a. QTcF interval >450 ms for men and >470 ms for women, symptomatic bradycardia <45 beats per minute or other significant ECG abnormalities in the investigator's opinion.
    b. Clinically uncontrolled hypertension in the investigator's opinion (e.g., blood pressure >160/100 mmHg; note that isolated elevated readings considered to not be indicative of uncontrolled hypertension are allowed).

    The following within 6 months prior to Cycle 1 Day 1:

    c. Congestive heart failure (New York Heart Class III or IV (see Appendix D)).
    d. Arrhythmia or conduction abnormality requiring medication. Note: patients with atrial fibrillation/flutter controlled by medication and arrhythmias controlled by pacemakers are eligible.

e. Severe/unstable angina, coronary artery/peripheral bypass graft, or myocardial infarction.

f. Cerebrovascular accident or transient ischemia.

12. Patients who are immunosuppressed (including known HIV infection), have a serious active infection at the time of treatment, have interstitial lung disease/pneumonitis, or have any serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. Patients with controlled hepatitis C, in the investigator's opinion, are allowed. Patients with known hepatitis B must be HBeAg and HB viral DNA negative for enrollment. Note that, because of the high prevalence, all patients in the AsiaPacific region (except Australia, New Zealand, and Japan) must be tested and, if HBsAg positive, must be HBeAg and HB viral DNA negative for enrollment.
13. Known hypersensitivity to tartrazine, a dye used in the ensartinib 100 mg capsule.
14. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
15. Concurrent condition that in the investigator's opinion would jeopardize compliance with the protocol or would impart excessive risk associated with study participation that would make it inappropriate for the patient to be enrolled.
16. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.

Note the following pertains to patients enrolled in France

17. Specific to France: Subjects will not be eligible when under legal protection.

6. TRIAL REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of this protocol and consent form are required.

7. ADMINISTRATION OF STUDY DRUG

All patients entering this study will receive ensartinib 225 mg QD or crizotinib 250 mg BID. Patients may take study medication (ensartinib or crizotinib) with or without food, although it should be noted that ensartinib is better tolerated with food.

The time of day for administration of study medication should be consistent. For patients participating in PK sampling, on scheduled PK collection days the patient should be instructed to wait until he/she arrives at the study center to take their study medication when instructed.

If the patient misses a dose of study medication, the patient should take the dose as soon as possible, but not less than 12 hours before the next dose is due for ensartinib and not less than 6 hours before the next dose is due for crizotinib. If the next dose is due in less than 12 hours for ensartinib or 6 hours for crizotinib, the patient should skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking the study medication, the patient should be instructed not to retake the dose. Patients should take the next scheduled dose of study medication. If vomiting persists, the patient should contact the investigator.

-No routine prophylactic antiemetics will be given. However, antiemetics may be administered with nausea and vomiting when they occur, and may be given prophylactically afterwards.

If the patient is to undergo a surgical procedure during the trial, study drug should be held the day before the procedure and may be resumed when the patient is allowed to receive, and is able to tolerate, oral medications.

If radiation is given during the trial (see Section 7.1), study drug should be held on days that the radiation is given.

7.1. Supportive Care

Use of erythropoietin replacement or bisphosphonates is considered supportive care, as is denosumab, and their use is permitted at the investigator's discretion.

Prophylactic granulocyte colony-stimulating factor (G-CSF) is prohibited. However, at the discretion of the treating physician, patients may receive therapeutic G-CSF if neutropenia occurs. Therapeutic use of G-CSF should follow standard American Society of Clinical Oncology (ASCO) or European Society of Medical Oncology (ESMO) guidelines.

Transfusions and antibiotics/antifungal agents, and other medications/treatments not prohibited by the protocol may be given, based on standard criteria and clinical judgment.

Patients are permitted to receive palliative radiation therapy at the discretion of the treating physician for bone metastases or isolated CNS metastases if there is no evidence of progressive disease elsewhere and the investigator feels that the patient would benefit from continued participation in the study. However, this must be discussed with, and agreed to, by the Medical Monitor. Note that sufficient information on the patient's disease status must be available to allow for this determination. If radiation is given during the trial, study drug should be held on days that the radiation is given.

Because crizotinib and other ALK TKIs may have phototoxicity potential, and as no phototoxicity studies have been performed for ensartinib, patients should be advised to take UV-light exposure minimization measures.

Severe visual loss has been reported in patients receiving crizotinib. Any patient that experiences severe visual loss (best corrected vision less than 20/200 in one or both eyes) or other serious visual complaints should have an ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of severe visual loss. There is insufficient information to characterize the risks of resumption of treatment in patients with a severe visual loss; a decision to resume treatment should consider the potential benefits to the patient.

7.2. Prior Treatment

Information on prior systemic therapy, radiation therapy, and surgery for the underlying disease, including start and stop dates and response to therapy, will be recorded on the electronic case report form (eCRF). In addition, information on other relevant medications, including supplements and herbal medications/products, and non-pharmacologic treatments/interventions taken or received by the patient within 14 days prior to the first dose of study drug will be recorded in the eCRF.

7.3. Concomitant Medications

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he/she is taking or has taken after the start of the study drug.

7.3.1. Prohibited Concomitant Medications

The following treatments are prohibited while on the clinical trial: any cancer treatment other than the study medication (note that the use of crizotinib, other than its use as study medication for patients randomized to receive crizotinib, is prohibited), including radiation therapy (except for palliative radiation therapy, as noted under Supportive Care), chemotherapy, hormonal therapy for cancer, cancer immunotherapy or other biologic therapy. The following are also prohibited:

- No other investigational therapy should be given to patients.
- Escalating doses of systemic corticosteroids for CNS metastases.
- Immunosuppressive agents.
- Drugs that are CYP3A substrates with narrow therapeutic indices (including, but not limited to, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).
- Drugs that are strong CYP3A inhibitors (including but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, and voriconazole). Also avoid grapefruit or grapefruit juice. While not prohibited, exercise caution with concomitant use of moderate CYP3A inhibitors.
- Drugs that are strong CYP3A inducers (including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort).
- Systemic use of anticancer herbal preparations/medications.

7.3.2. Concomitant Medications to Be Used with Caution

The following should be used with caution:

- Medications (including antiarrhythmics) known to cause bradycardia (including, but not limited to, beta-blockers, non-dihydropyridine, calcium channel blockers, clonidine, and digoxin) or QT interval prolongation (see Appendix C) should be

avoided, if possible. If required, these should be used with caution and the patients carefully monitored.

- As crizotinib may have the potential to increase plasma concentration of drugs metabolised by CYP2B6 (including, but not limited to, bupropion, efavirenz), such drugs should be used with caution in patients taking crizotinib.
- As ensartinib inhibits CYP2C9, drugs metabolised by CYP2C9 (including, but not limited to celecoxib, glimepiride, phenytoin, tolbutamide, warfarin) should be used with caution in patients taking ensartinib.

8. DOSE MODIFICATIONS

Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. Note that if dose reduction is subsequently determined to have not been necessary (e.g., change in assessment of causality of an AE that had led to dose reduction), dose escalation back to the previously given dose level can be discussed with the Medical Monitor. Patients whose treatment is delayed due to toxicity will discontinue study drug or will resume treatment when toxicity has improved (as long as the toxicity resolves within 4 weeks) according to the dose modifications below.

Dose reductions for toxicity or based on the clinical judgment of the treating physician will be allowed. If persistent toxicity occurs despite the dose reductions, the investigator should consider removing the patient from the study.

Any patients who require a treatment delay of more than 4 weeks due to treatment-related toxicity will be discontinued from trial treatment. Toxicity will be graded using National Cancer Institute Common Terminology for Adverse Events (NCI CTCAE) v4.03.

8.1. Dose Reductions

Up to 2 dose reductions are allowed. If unable to tolerate study medication despite 2 dose reductions, patients should be discontinued from trial treatment.

	Ensartinib	**Crizotinib**
First Dose Reduction	200 mg QD	200 mg BID
Second Dose Reduction	150 mg QD	250 mg QD

8.2. Dose Modifications Due to Drug-related Hematologic Toxicity (Ensartinib and Crizotinib)

If drug-related hematologic toxicity occurs, treatment should be held (see Table 1) and reevaluated in at least 1 week. Absolute neutrophil count (ANC) and platelets should be monitored as is clinically appropriate, but at least weekly, until recovery. For resumption of treatment, see Table 1. If ANC and/or platelets do not recover within 4 weeks the patient should be permanently discontinued from trial treatment.

Table 1: Dose Modifications Due to Drug-related Hematologic Toxicities

Event	Study Medication [a]
Grade 3	
ANC <1.0 x 10^9/L or platelets <50 x 10^9/L	Hold dose until recovery to ≤ Grade 2 [ANC ≥1.0 x 10^9/L or platelets to ≥50 x 10^9/L], then resume at same dose level
Grade 4	
ANC <0.5 x 10^9/L or platelets <25 x 10^9/L	Hold dose until recovery to ≤ Grade 2 [ANC ≥1.0 x 10^9/L or platelets to ≥50 x 10^9/L], then resume at next lower dose level

[a] Any patients who require a treatment delay of more than 4 weeks due to treatment-related toxicity will be discontinued from trial treatment.

8.3. Dose Modifications Due to Drug-related Non-Hematologic Toxicities (Ensartinib and Crizotinib)

8.3.1. Grade 3 or 4 Non-Hematologic Toxicity

The dose reduction guidelines for drug-related non-hematologic toxicities are shown in Table 2 and Table 3. If a Grade 3 non-hematologic toxicity that is expected to be manageable and reversible with dose reduction occurs, treatment with study should be held until the toxicity resolves to ≤ Grade 1. If the Grade 3 non-hematologic toxicity lasts longer than 7 days, study drug will be discontinued. Patients with Grade 3 non-hematologic toxicity lasting ≤7 days that does not resolve to ≤ Grade 1 within 4 weeks should also be removed from the trial treatment. If a Grade 4 non-hematologic toxicity occurs, study drug should be discontinued in most cases. However, in the case of either Grade 3 toxicity lasting longer than 7 days or Grade 4 toxicity, if the investigator feels that it is appropriate for the patient to continue in the study, this must be discussed with the Medical Monitor. If it is agreed by both the investigator and Medical Monitor that the patient can remain on study, the remaining guidelines for Grade 3 toxicity should be followed.

Table 2: Dose Modification Guidelines for Drug-related Non-Hematologic Toxicities

Toxicity Grade	Study Drug
Grade 0, 1, or 2	None
Grade 3 and expected to be manageable and reversible with dose reduction	Hold [a]
If toxicity remains Grade 3 toxicity for longer than 7days	Discontinue study drug (however, see text above)
If Grade 3 toxicity lasts ≤ 7 days and resolves to ≤ Grade 1	Reduce one dose level
Grade 3 and not expected to be manageable and reversible with dose reduction (e.g., cardiac failure)	Discontinue study drug
Grade 4	Discontinue study drug (however, see text above)

[a] Study drug should be held until toxicity resolves to ≤ Grade 1. Any patient who develops toxicity that does not resolve to ≤ Grade 1 within 4 weeks should be removed from the trial treatment.

Table 3: Specific Guidelines

Criteria	Study Drug
Crizotinib: ALT or AST elevation >5 times ULN with total bilirubin ≤1.5x ULN Ensartinib: ALT or AST elevation >5 times ULN with total bilirubin ≤2x ULN	Withhold until recovery to baseline or ≤3x ULN, then resume at a one dose level reduction
Crizotinib: ALT or AST elevation >3x ULN with concurrent total bilirubin elevation >1.5x ULN (in absence of cholestasis or hemolysis) Ensartinib: ALT or AST elevation >3x ULN with concurrent total bilirubin elevation >2x ULN (in absence of cholestasis or hemolysis)	Permanently discontinue unless a correctable, non-drug related cause of the liver test evaluations can be documented
Any grade drug-related interstitial lung disease/pneumonitis (not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect)	Permanently discontinue

Study Drug:
Date of

QTcF >500 ms on at least 2 separate ECGs	Withhold until recovery to baseline or to a QTcF <481 ms, then resume at reduced dose
QTcF >500 ms or ≥60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue
Bradycardia[a] (symptomatic, may be severe and medically significant, medical intervention indicated)	Withhold until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above Evaluate concomitant medications known to cause bradycardia, as well as antihypertensive medications If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, resume at reduced dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above
Bradycardia [a,b] (life-threatening consequences, urgent intervention indicated)	Permanently discontinue if no contributing concomitant medication is identified If contributing concomitant medication is identified and discontinued, or its dose is adjusted, resume at reduced dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring
Visual Loss (Grade 4 Ocular Disorder)	Discontinue during evaluation of severe vision loss. Any patient that experiences severe visual loss (best corrected vision less than 20/200 in one or both eyes) or other serious visual complaints should have an ophthalmological evaluation consisting of best corrected visual acuity, retinal photographs, visual fields, optical coherence tomography (OCT) and other evaluations as appropriate for new onset of severe visual loss. There is insufficient information to characterize the risks of resumption of treatment in patients with a severe visual loss; a decision to resume

	treatment should consider the potential benefits to the patient.
Rash For rash severity, rather than using CTCAE criteria based on BSA, consider severity based on symptoms and intensity. For mild (grade 1): For moderate and symptomatic (grade 2): For severe (grade 3) [c]:	Continue treatment at same dose, follow, and if necessary, use topical treatments. Continue treatment at same dose; topical steroids may be used. If after 1 week the rash is worse or there is no improvement, give a 5 day course of tapering oral steroids. If 1 week later it is not improved to ≤ grade 1, hold drug until ≤ grade 1. At that time, resume ensartinib at a 1 dose level reduction. Hold therapy. Topical treatments may be used. Oral corticosteroids can be considered. When ≤ grade 1, resume at 1 level dose reduction. Note: Antibiotics should not be given routinely unless rash is acneiform/pustular
Grade 3 nausea, vomiting, and/or diarrhea	Study drug should be held and supportive care initiated Follow guidelines in Table 2
Severe renal dysfunction (CL <30 mL/min) not requiring dialysis **(Note: this only pertains to severe renal impairment not thought to be related to study medication. If thought to be drug-related, follow guidelines in Table 2.)**	Crizotinib: 250 mg QD. The dose may be increased to 200 mg BID based on individual safety and tolerability after at least 4 weeks of treatment. When CL improves to ≥50 mL/min, dose may be escalated back to the pre-dose modification level, if appropriate. Ensartinib: Hold dose until creatinine clearance returns to < grade 3 (CL ≥30 mL/min). If this occurs within 4 weeks, resume at a 1 level dose reduction. When CL improves to ≥50 mL/min, dose may be escalated back to the pre-dose modification level, if appropriate.
[a] Heart rate < 60 beats per minute (bpm) [b] Permanently discontinue for recurrence [c] For drug-related rash skin biopsy and digital photos are encouraged	

9. TRIAL ASSESSMENTS AND TREATMENT

9.1. Overview

All patients will take ensartinib and crizotinib orally as capsules. The dosing frequency for ensartinib will be once daily, and for crizotinib it will be twice daily (once daily if needed for dose reduction).

A cycle of treatment is scheduled to last approximately 4 weeks (28 calendar days). Multiple procedures may be scheduled at the same time point relative to study drug dosing. Priority should be given to PK collection at the time specified for those patients participating in PK sampling. Vital signs and ECG assessments should be performed prior to blood specimen collections.

All patients should visit the study center on the days specified within this protocol. Very unsual circumstances, e.g. global disasters or pandemics including COVID-19 ongoing one, may prevent full compliance to visit schedule, however, during normal periods every effort should be made to comply. The complete Schedule of Assessments for this trial is shown in Appendix E; details on the timing of assessments can be found there.

9.2. Screening

Informed consent must be obtained ≤28 days prior to initiation of treatment and before any protocol-specific procedures are performed. Screening assessments described in Appendix E will be collected, reviewed, and determined to be acceptable by the site Principal Investigator (PI) or designee after obtaining informed consent and ≤28 days prior to initiation of treatment. If these initial examinations are obtained within 72 hours (or as otherwise noted) of Cycle 1 Day 1, they do not have to be repeated. Scans for disease assessment should be performed ≤28 days prior to initiation of treatment. Patients that fail screening initially may be allowed to rescreen at a later date.

9.3. Trial Treatment Period

Patients will visit the study center on approximately Day 15 of Cycle 1 and Day 1 of each cycle (i.e., every 28 ± 3 calendar days or every 12 weeks ± 1 week starting at Cycle 19 due to impact of COVID-19 pandemic) and at other times as specified. All visits should occur as close as possible to the protocol specified time. Complete listings of the assessments that will be performed at each visit during the trial treatment period are specified in Appendix E.

9.4. End of Trial Treatment

Patients are permitted to continue treatment with study drug until disease progression, or the patient is discontinued due to unacceptable toxicity or a decision to discontinue treatment by the patient or the trial physician. Follow-up evaluations required after treatment ends are specified in Appendix E.

If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no trial treatment is administered, that visit may fulfill the End of Treatment Visit.

After withdrawal from or completion of protocol treatment, patients must be followed for any new AEs for 30 calendar days after the last dose of trial drug.

Study Drug:
Date of

For **Belgium and Germany**, a 30 day post treatment pregnancy test must be performed in women of childbearing potential.

For patients who discontinue treatment without radiographic progression per RECIST 1.1 (e.g., in patients who discontinue treatment for clinical disease progression or adverse reactions), disease assessments should continue approximately every 8 weeks (or every 12 weeks ± 1 week starting at Cycle 19 due to impact of COVID-19 pandemic) after study treatment until radiographic disease progression or alternate therapy is given.

After the completion of study treatment, patients will be followed for survival. This should be done approximately every 6 months. Note: patients that end treatment for reasons other than disease progression should continue to be followed every 8 weeks (or every 12 weeks ± 1 week starting at Cycle 19 due to impact of COVID-19 pandemic). Once disease progression occurs per RECIST criteria, then follow for survival approximately every 6 months.

9.5. Early Patient Termination / Patient Withdrawal

Patients who discontinue treatment early due to disease progression or withdrawal will be asked to have all end of trial treatment safety evaluations performed as described in the protocol.

9.6. Safety Assessments

Safety assessments will consist of monitoring and recording protocol-defined AEs and serious adverse events (SAEs), measurement of protocol-specified hematology, clinical chemistry, coagulation, and urinalysis variables, measurement of protocol-specified vital signs, ECGs, and other protocol-specified tests that are deemed critical to the safety evaluation of the trial drug. Very unsual circumstances, e.g. global disasters or pandemics as the COVID-19 pandemic, may prevent full compliance to visit schedule. During such periods, since trial participants may not be able to come to the investigational site for protocol-specified visits, other means to access patient safety may be used, e.g. virtual visits, valid patient information from local (non-study site) healthcare facilities, PI risk assessments with the prirotity to ensure the safety of trial participants.

9.6.1. Adverse Events

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.03 (CTCAE) will be used to assess the severity of AEs (see Section 14.1.1).

9.6.2. Laboratory Tests

*** Denotes not required where confirmed by CRO that local laboratory does not have the capability.**

9.6.2.1. CBC plus Differential and Platelets

The following laboratory tests must be performed for assessment of CBC plus differential and platelets:

- white blood cell count plus differential (total neutrophil count, lymphocytes, monocytes)

- hemoglobin
- hematocrit*
- platelets

9.6.2.2. Clinical Chemistry

The following laboratory tests must be performed for assessment of clinical chemistry:

- glucose
- blood urea nitrogen (BUN)*
- creatinine
- sodium
- potassium
- magnesium
- chloride
- calcium
- carbon dioxide (CO2)*
- alkaline phosphatase
- AST (SGOT)
- ALT (SGPT)
- total bilirubin
- total protein
- albumin
- phosphorus
- uric acid

9.6.2.3. Coagulation Measurements

The following laboratory tests must be performed for assessment of coagulation:

- Prothrombin Time (PT)*
- Partial Thromboplastin Time (PTT)*
- International Normalized Ratio (INR)*

9.6.2.4. Testosterone Monitoring

Total testosterone levels will be monitored in male patients*.

9.6.2.5. Urinalysis

A urine dipstick (pH, specific gravity, blood, protein, glucose) will be performed.

9.6.2.6. Serum or Urine Pregnancy Test

For women of childbearing potential only, a serum or urine pregnancy test will be performed within 1 week prior to initial treatment, during treatment if a menstrual cycle is missed or pregnancy is otherwise suspected, and at the end of treatment visit.

Note: In addition to the above, for countries where it is required (e.g., **Belgium, U.K., Poland and Germany**), beginning with Cycle 2, pregnancy testing must also be performed on the Day 1 assessment of every cycle, and in **Belgium/Germany** 30 days after the end of treatment, in women of childbearing potential.

9.6.2.7. Hepatitis B Testing

As noted in Exclusion Criterion #13, patients with known hepatitis B must be HBeAg and HB viral DNA negative for enrollment. Because of the high prevalence, all patients in the Asia-Pacific region (except Australia, New Zealand, and Japan) must be tested and, if HBsAg positive, must be HBeAg and HB viral DNA negative for enrollment.

9.6.3. Other Safety Assessments

9.6.3.1. 12-Lead Electrocardiograms

Three 12-lead electrocardiograms (ECGs) will be collected approximately 5 minutes apart at the specified times. Note that ECGs should be obtained before blood collection. ECGs will be evaluated locally for safety but will also be evaluated by eResearch Technology, Inc. (ERT).

Virtual safety assessments during COVID-19 pandemic

During the COVID-19 pandemic (and as well in similar situations of global disasters) patients that cannot reach the investigational site nor a local health care facility to perform the above listed laboratory tests and EKG as planned by a scheduled visit by protocol could be evaluated by the investigator with a virtual visit. Before receiving study drug safety must be paramount and ensured based on patient history on drug and current symptoms and sings. Investigator and site must then document the findings in the clinical chart and consequent decision on study drug administration.

9.6.4. Efficacy Assessments

9.6.4.1. Restaging

Patients will be restaged at approximately 8-week intervals (approximately every 2 cycles) during trial treatment. However, beginning at Cycle 19, the interval will increase to every 12 weeks (+/- 1 week) due to impact of COVID-19 pandemic. For a best response of CR or PR, the response must be documented to have lasted for a minimum of 4 weeks, i.e., on 2 assessments performed at least 4 weeks apart. Patients with progressive disease or unacceptable toxicity should be discontinued from study drug unless it is thought to be in the patient's best interest to remain on treatment and this has been allowed by the Medical Monitor, as discussed elsewhere in the protocol. For patients who discontinue treatment without radiographic progression per RECIST 1.1 (e.g., in patients who discontinue treatment for clinical disease progression or adverse reactions), disease assessments should continue approximately every 8 weeks after

discontinuation of study treatment until radiographic disease progression or alternate therapy is given. As above, beginning at Cycle 19, the interval will increase to every 12 weeks (+/- 2 weeks) due to impact of COVID-19 pandemic. The assessments that will be performed at each visit during the trial treatment period are specified in Appendix E. In case patients cannot perform the required scan as during the COVID-19 pandemic, efforts should be made to have a scan taken at a local facility and send it to the investigational site to be then transmitted for central read. If this is not possible the scan will be skipped and recorded as a deviation and schedule will be resumed at next possible visit.

9.6.4.2. Quality of Life Assessments

Quality of life will be assessed by the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale. For consented patients during unsual circumstances, e.g. global pandemics, and unable to provide quality of life assessments these will not be protocol deviations.

9.7. Pharmacokinetic Assessments

Sparse PK sampling will be performed at selected sites in this trial. To characterize exposure differences in Asian populations, PK sampling will be required at sites in China. PK blood samples will be collected from patients receiving ensartinib pre-dose and approximately 4 hours (± 1 hour) after dosing on Cycle 1 Day 1 and Cycle 2 Day 1, pre-dose on Cycle 3 Day 1, and at the end of treatment visit if the patient had taken the last dose of study drug the day before the end of treatment visit. For consented patients during unsual circumstances, e.g. global pandemics, and unable to provide samples these will not be protocol deviations.

Note: A random PK sample may be drawn at any time during the trial if it is felt that it may be helpful in assessing the safety of the patient.

See Laboratory Manual for handling and shipping instructions.

9.8. Pharmacogenetic Assessment

A sample will be collected from as many ensartinib patients as possible at baseline for possible pharmacogenetic evaluations. For consented patients during unsual circumstances, e.g. global pandemics, and unable to provide samples these will not be protocol deviations.

See Laboratory Manual for handling and shipping instructions.

9.9. Biomarkers

The analyses for biomarkers are exploratory. Testing may include sequencing of ALK kinase domain pre-treatment, NGS or RT-PCR to detect fusion variants, detection of ALK fusions as circulating DNA, analysis of skin biopsies if rash develops, and other assessments. The results may be pooled with data from other studies to generate hypotheses to be tested in future studies. For consented patients during unsual circumstances, e.g global pandemics, and unable to provide samples these will not be protocol deviations.

9.9.1. Assessment of Tumor Tissue Samples

Patients entering this study will be required to provide adequate tissue (archival and/or fresh biopsy) for eligibility and correlative testing. Optional on-study biopsies taken at the time of

disease progression will also be requested for correlative testing. See Laboratory Manual for handling and shipping instructions for the tissue samples. Informed consent for tissue for correlative testing must be obtained.

Patients will be allowed to enroll based on ALK testing performed centrally using an FDAapproved assay. Testing for other targets, such as MET, KRAS, EGFR, or others, may be performed on samples on an exploratory basis.

9.9.2. Biomarker Blood Samples for ALK and Treatment Response Testing

During treatment, optional biomarker blood samples will be taken for exploratory evaluation of nucleic acids (such as DNA, RNA) and/or proteins at the below time points. For consented patients during unsual circumstances, e.g. global pandemics, and unable to provide samples these will not be protocol deviations.

- **Cycle 1 Day 1**: pre-dose
- **Day 1 of Each Cycle from Cycle 2** through End of Trial Treatment
- **End of Trial Treatment**

At these time points, approximately 10 mL of blood will be collected in each of 2 EDTA tubes (total of approximately 20 mL of blood). In addition to testing for ALK, other resistance mechanisms may be evaluated. See Laboratory Manual for handling and shipping instructions.

10. INVESTIGATIONAL PRODUCTS

Study Drug	Dosage Form and Strength	Manufacturer
Ensartinib	25 mg and 100 mg, capsules	Xcovery
Crizotinib	250 mg and 200 mg, capsules	Pfizer

Study drug will be administered orally as capsules.

Additional information on ensartinib can be found in the ensartinib IB, and additional information about crizotinib can be found in the crizotinib prescribing information.

10.1. Labeling, Packaging, and Supply

Ensartinib capsules will be supplied in 2 strengths: 25 mg and 100 mg. Ensartinib capsules are packaged in HDPE bottles with child resistant induction seal caps. Thirty capsules are included in each bottle.

Study drug will be labeled as required by all applicable regulations. The investigator or delegated site staff will ensure that all investigational product is stored in a secured area under recommended storage conditions and in accordance with applicable regulatory requirements. Ensartinib capsules will be stored at room temperature, 15°C to 30°C (59°F to 86°F). Any

excursion above 30°C will be reported to the Sponsor. A temperature log must be maintained at each study site. Ensartinib is not to be refrigerated or frozen.

Upon randomization to the ensartinib arm, the clinical site pharmacist will initially dispense 225mg of ensartinib, then appropriate amount during subsequent visits. An appropriate number of 30 capsule containers should be dispensed for the patient's treatment until the next visit (and potential overage to maintain their dosing routine). Any unused study drug must be returned to the site. If there is concern about risk of exposure to COVID-19, home delivery of investigational product that would not raise any new safety risks may be implemented to protect patients from coming to clinical trial sites. In all cases, requirements under FDA regulations for maintaining required investigational product storage conditions and investigational product accountability remain.

Note that crizotinib will be supplied by the Sponsor. Crizotinib will be supplied in either cartons or bottles depending on it's manufacturing location.

The Sponsor or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

11. Preparation and Administration of Investigational Products

12. Study Drug

Study drug will be self-administered by the patient. The investigator or authorized designee will provide verbal dosing instructions prior to dispensing.and appropriate instructions incorporated on the bottle label. This discussion should be documented in the source documents.

During unsual circumstances, e.g. global pandemics, alternative formats for instructions (phone calls, emails, etc.) may be used, but also documented.

12.1. Accountability, Reconcilation and Return of Investigational Products

The PI (or designee) is responsible for accountability of all used and unused trial drug supplies at the site.

The site monitor will verify receipt of investigational product at the site during monitoring visit(s), and will conduct an inventory of remaining clinical trial supplies at the site close-out visit. All trial drug inventories must be made available for inspection by the monitor, Sponsor, or representatives of the aforementioned and regulatory agency inspectors upon request.

At the end of the trial, a "Return Drug Form" will be completed by the site and will accompany the clinical trial supplies that are returned to the Sponsor (or designee). Clinical trial supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative.

12.2. Precautions and Risks Associated with Study Drug

Refer to the Investigator Brochure for details of the risks associated with the use of ensartinib and to the prescribing information for details about the risks associated with the use of crizotinib.

13. RESPONSE EVALUATIONS AND MEASUREMENTS

13.1. Definitions

13.1.1. Systemic Disease and CNS Disease Evaluated by RECIST

Response and progression will be evaluated in this trial using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Two separate outcomes will be determined by the sites. The outcomes will include a standard RECIST 1.1 evaluation of all sites of disease (systemic as well as CNS), for the purpose of this protocol to be called RECIST 1.1 Combined Outcome, as well as a separate RECIST 1.1 CNS outcome that will encompass only brain lesions. The approach to both will be the standard application of the RECIST 1.1 criteria, with the difference in the 2 outcomes centered on the anatomic sites of disease from which target, non-target and new lesions are identified. The standard approach and definitions of response and progression will remain the same for both outcomes.

In the standard approach to RECIST 1.1, all sites of disease should be identified at baseline and categorized as being measurable or non-measurable as described below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Measurable Disease:	• Non-nodal lesions must be accurately measured in the longest diameter (LD), outer diameter to outer diameter generally in the axial plane with a minimum size of:
	  • 10 mm by computerized tomography (CT) scan or MRI (provided the CT scan slice thickness is no greater than 5 mm or the MRI slice thickness is no greater than 5.0 mm with no gap between slices). Note: For this study, MRI may be used as an alternative to CT of the abdomen and pelvis.
	  • CNS lesions can be either enhancing or non-enhancing lesions. Enhancing lesions are preferable. Nonenhancing lesions should only be lesions that represent tumor, as other benign etiologies can be seen as regions of high signal on T2/FLAIR images.
	• Lymph nodes require special consideration. Nodal lesions must be accurately measured in the Short Axis Dimension (SAD) and must measure ≥ 15 mm to be considered measurable. At baseline and in follow-up, only the SAD will be measured on nodal lesions.

Non-Measurable Disease:	All other lesions identified at baseline that do not meet the size criteria for measurable lesions are considered non-measurable lesions, including:

	• Non-nodal lesions that have a LD <10 mm. • Lymph nodes that are considered pathologic but do not meet the size criteria for measurable disease (this includes lymph nodes that are ≥ 10 mm SAD but < 15 mm SAD. • Lesions that are considered truly non-measurable, including: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. • Note: bone scan, 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.
Target Lesions:	Target lesions are selected at baseline from those lesions that meet the criteria for measurable disease. Criteria for inclusion of lesions as target lesions include: • Target lesions should be selected on the basis of their size (generally the lesions with the longest diameter). • Target lesions should be representative of all involved organs and represent the full extent of disease. • Target lesions should be the most reliably and reproducibly measurable lesions. • Target lesions can be chosen from sites that have previously been treated by local therapy including, but not limited to, radiofrequency ablation (RFA), hepatic chemo-embolization or radiation therapy, if there has been documented progression of tumor in the treated field after completion of the therapy. If locally treated lesions have not progressed, those lesions can be considered nontarget lesions. • Concerning cystic lesions: ▪ Radiographically benign simple cysts are by definition benign and therefore should not be considered as either target or non-target lesions. ▪ Complex cystic lesions that could represent cystic metastases can be considered as target lesions if they meet the criteria for measurable lesions. However, in the situations where there are solid lesions and cystic lesions, the solid lesions should be preferentially chosen as target lesions. • The number of target lesions selected should be: ▪ For the RECIST 1.1 Combined assessment, up to a maximum of 5 target lesions in total, up to a maximum of 2 per organ should be selected. Note: Lymph nodes are considered a single organ system, so only 2 nodes should be selected as target lesions.

	▪ For the RECIST 1.1 CNS assessment, up to a maximum of 5 CNS target lesions should be selected. ▪ Target lesions should be intra-parenchymal brain metastases or dural based brain metastases ▪ Note: For the purpose of this specific selective RECIST 1.1 CNS assessment, skull lesions, skull based lesions (with or without intracranial extension) and intra-dural spinal lesions will not be considered as target lesions. ▪ Dural based lesions resulting from a skull metastasis are not considered target lesions. Dural based lesions thought to represent metastases to the dura at baseline can be considered as target lesions if they meet the criteria for measurable disease. In a patient with parenchymal and dural based lesions, parenchymal lesions are preferred for choice of target lesion. If they do not meet the size criteria, they can be considered non-target lesions.
Non-Target Lesions:	All other sites of disease identified at baseline, not chosen as target lesions, should be identified as non-target lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up and will contribute to the assessment of response or progression.

13.2. Guidelines for Evaluation of Measurable Disease

13.2.1. Combined RECIST 1.1 Assessment (Systemic Disease and CNS Disease Evaluated by RECIST)

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Actual target lesion size should be measured. If a target lesion disappears, record the measurement of 0 mm. However, if the target lesions are visible but too small to measure accurately, a default value of 5 mm should be used for that measurement. Nodal target lesions should be measured by the SAD. The SAD of the nodal lesions should be recorded even if the node becomes normal (measuring < 10 mm SAD).

If target lesions coalesce during treatment such that they are no longer separable, the maximum longest diameter for the coalesced lesion should be determined and that measurement should be used for the LD. Similarly, if nodal lesions coalesce, the SAD of the coalesced lesion should be used as the SAD.

If a target lesion separates to form discrete lesions on a subsequent imaging time point, the longest diameter of each lesion should be measured, summed and the summed measurement reported as the LD for that lesion. Similarly, if a nodal target lesion separates to form discrete lesions on a subsequent imaging time point, the SAD of each lesion should be measured, summed and the summed measurement reported as the SAD for that lesion.

Systemic Disease

CT and MRI:	CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. CT scan should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. (Note: For this study, MRI may be used as an alternative to abdomen and pelvis CT scans.) Head and neck tumors and those of extremities usually require specific protocols.
Cytology and Histology:	Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

13.2.2. CNS RECIST 1.1 Assessment of Intraparenchymal CNS Metastases

MRI:	The same method and technique used at baseline should be used throughout. Gadolinium-enhanced MRI should be used unless contraindication for MRI, in which case CT with and without contrast may be used. Slices ≤5 mm apart (ideally ≤1.5 mm apart) with 0 mm skip, T1 pre- and post-contrast.

13.3. Response Criteria

13.3.1. Combined RECIST 1.1 Assessment and CNS RECIST 1.1 Assessment

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. For the Combined RECIST 1.1 Assessment that may include target lesions, any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. Note that the longest diameter should be used for all non-lymph node target lesions, and the short axis should be used for lymph nodes.

Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum LD since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.
Not Evaluable (NE):	NE can be applied if repeated measurements cannot be assessed for reasons such as inadequate or missing imaging.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions. For the Combined RECIST 1.1 Assessment that may include nodal non-target lesions, all lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When patient also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, overall tumor burden has increased sufficiently to merit discontinuation of therapy.
Not Evaluable (NE):	NE can be applied if evaluations cannot be assessed for reasons such as inadequate or missing imaging.
Not Applicable (NA):	Absence of any non-target lesion if no non-target lesions at baseline.

Time Point Response

The Time Point Response is the response assessed at each assessment point and is derived from the contribution of the target lesions response, the non-target lesions response and the presence or absence of new lesions, according to the table/algorithm below. This will be reported for the RECIST 1.1 Combined Assessment and the RECIST 1.1 CNS Assessment.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	CR, Non-CR/Non-PD, NA or NE	No	PR
SD	CR, Non-CR/Non-PD, NA or NE	No	SD

Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

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 "zero" on the eCRF.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Fluid collections (i.e., pleural effusions, pericardial effusions and ascites):

- Recurrent Effusion/Ascites**:** a fluid collection that was present at Screening, but which subsequently disappeared and then recurred, will not be considered a new lesion, nor will it be assessed as progressive disease, unless the treating physician determines that the increase is significant to be consistent with unequivocal PD.
- New Effusion/Ascites: The appearance of a new fluid collection that is thought to be unequivocally malignant should be called PD. Cytology is not required in this instance, but would provide definitive proof of progression.

Progression in bone:

- New areas of increased tracer uptake or pre-existing areas of abnormal increased tracer uptake on bone scans that demonstrate a greater level of activity on subsequent scans should not be considered progression unless there is direct correlation with cross sectional imaging techniques that there has been an increase in the size of the corresponding bone lesion.
- Note that blastic lesions and new sclerotic lesions need to be evaluated carefully, since they could represent a positive treatment effect.

13.3.2. Best Overall Response

The best overall response is the best time point response recorded from the date of randomization until disease progression/recurrence. The patient's best overall response assignment for the

RECIST 1.1 Combined Assessment and the RECIST 1.1 CNS Assessment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

For a best response of CR or PR, the response must be documented to have lasted for a minimum of 4 weeks, i.e., on 2 assessments performed at least 4 weeks apart.

14. SAFETY REPORTING AND ANALYSES

14.1. Adverse Events

The PI is responsible for recognizing and reporting adverse events to the Sponsor or its representative. It is the Sponsor's or its representative's responsibility to report relevant SAEs to the applicable local, national, or international regulatory body.

14.1.1. Definitions of Adverse Events

Adverse Event: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (For the purposes of this definition, ''untoward'' means unfavorable, negative, or harmful). An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Suspected Adverse Reaction: Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Please note: Do not confuse with European Medicines Agency designation of Serious Adverse Reaction (SAR) discussed in section 12.2. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

The following are examples of types of evidence that would suggest a causal relationship between the drug and the adverse event (i.e., that there is a reasonable possibility that the drug caused the AE).

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, Stevens-Johnson Syndrome). The occurrence of even one case of such AEs would meet the definition of suspected adverse reaction.
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture, heart valve lesions in young adults, or intussusception in healthy infants). If the event occurs in association with other factors strongly suggesting causation (e.g., strong temporal association,

event recurs on rechallenge), a single case may be sufficiently persuasive to report in an IND safety report. Often, more than one occurrence from one or multiple studies would be needed before the Sponsor could determine that there is a reasonable possibility that the drug caused the event.

- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation [e.g., symptoms, disease progression] or other events that commonly occur in the study population independent of drug therapy [e.g., cardiovascular events in an elderly population]) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Adverse Reaction: An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.03 (CTCAE) will be used to assess the severity of AEs (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to their impact on the participant's ability to perform daily activities as described in the introduction to CTCAE v4.03 and the General Disorders and Administration Site Conditions system organ class (SOC).

14.1.2. Recording of Adverse Events

All AEs of any patient during the course of the trial will be reported in the eCRF, and the investigator will give his or her opinion as to the relationship of the AE to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration). AEs are to be recorded for each patient from their first dose of trial drug treatment. An event occurring after the patient has provided informed consent but before the first dose of study medication will be collected as part of the medical history. If a patient experiences a Serious Adverse Event (SAE) after signing informed consent, but prior to receiving study drug, the event does not need to be recorded as an SAE unless the investigator feels the event may have been caused by a protocol procedure. Other untoward events occurring in the framework of a clinical trial are also to be recorded as AEs.

All AEs regardless of seriousness or relationship to trial treatment, spanning from the start of trial treatment until 30 calendar days after discontinuation or completion of protocol-specific treatment as defined by the protocol for that patient, are to be recorded on the eCRF. However, once another anticancer therapy has been started, non-serious AEs during this time that are not thought by the investigator to be related to study treatment do not have to be reported.

14.1.3. Abnormal Laboratory Values and Vital Signs

The reporting of abnormalities of vital signs as AEs should generally be avoided. Abnormalities of vital signs generally should not be reported unless considered clinically significant or any criterion for an SAE is fulfilled, including being considered medically important or the vital

signs abnormalities cause the patient to discontinue trial treatment. Any Grade 3 or 4 laboratory abnormalities or any clinically significant Grade 1 or 2 laboratory value(s), ECG abnormalities or vital sign changes should be recorded as an AE. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF.

14.1.4. Handling of Adverse Events

All AEs should be followed until resolution or stabilization. Patients must be followed for any new AEs for 30 calendar days after discontinuation or completion of protocol-specific treatment. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF. After 30 days, only AEs, SAEs, or deaths assessed by the investigator as treatment-related are to be reported.

14.2. Serious Adverse Events (SAEs)

14.2.1. Definitions of Serious Adverse Events

The definitions of SAEs are given below. The PI is responsible for ensuring that all staff involved in the trial are familiar with the content of this section.

An SAE (or Serious Adverse Reaction, SAR) is defined as any AE or suspected adverse reaction that results in any of the following outcomes: death, is immediately life-threatening, requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/birth defect.

The definition of SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Death due to disease progression will be recorded on the appropriate eCRF and need not be reported as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit

- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care or respite care facility

Hospitalization during the trial for a pre-planned surgical or medical procedure (one which was planned prior to entry in the trial) or for social or administrative reasons (e.g., no place to stay, yearly physical) does not require reporting as an SAE to the CRO Safety Department.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when evaluating AEs and SAEs.

14.2.2. Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to the CRO Safety Department in order to comply with regulatory requirements. Serious AEs may occur at any time from start of trial treatment through the 30-day follow-up period after the last trial treatment (or beyond if considered related to trial treatment). The CRO Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.

The SAE will be reported by the CRO Safety Department to the Sponsor or designee within 1 business day of awareness of the event and as outlined in the Safety Monitoring Plan.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Sponsor or designee as soon as it is available. The detailed SAE reporting process will be provided to the sites in the Safety Monitoring Plan.

Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB)/Independent Ethics Committee (IEC) according to the policies of the responsible IRB/IEC.

Contact details for the IQVIA Biotech Safety Department are as follows: **IQVIA**

Biotech Safety Department

Phone:	
U.S.:	1-866-758-2798
Worldwide Safety Hotline:	1-919-313-7111
Fax:	
U.S.:	1-866-761-1274
Worldwide:	1-919-313-7111
Email:	safety-inbox.biotech@iqvia.com

Note that additional country-specific contact information may be provided separately.

14.2.3. Sponsor SAE Reporting Requirements

The Sponsor or designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with ICH guidelines, FDA regulations, and/or local regulatory requirements.

The assessment of whether an AE or suspected adverse reaction is ‘‘unexpected’’ (i.e., not listed in the investigator brochure or is not listed at the specificity or severity that has been observed) is assessed by the Sponsor. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The Sponsor or designee will notify all required Regulatory Agencies and all participating investigators in a written IND safety report of any suspected adverse reaction that, based on the opinion of the investigator or Sponsor, is serious and unexpected (based on the opinion of the Sponsor), as soon as possible, but in no case later than 15 calendar days after receipt by the Sponsor of the minimum data set for the suspected adverse reaction.

The Sponsor or designee will notify all required Regulatory Agencies and all participating investigators in a written IND safety report of any fatal or life-threatening suspected adverse reaction that, based on the opinion of the investigator or Sponsor, is serious and unexpected (based on the opinion of the Sponsor), as soon as possible, but in no case later than 7 calendar days after receipt by the Sponsor of the minimum data set.

The investigator’s judgement of relatedness will be used for the purpose of expedited reporting. The Sponsor may upgrade the consideration of relatedness for that purpose, but the judgement of the investigator will not be downgraded for the purpose of expedited reporting. The Sponsor will identify all safety reports previously filed with the IND concerning a similar suspected adverse reaction, and will analyze the significance of the suspected adverse reaction in light of the previous, similar reports.

14.3. Recording of Adverse Events and Serious Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the SAE Report Forms and AE eCRF. Avoid colloquialisms and abbreviations.

All AEs, including those that meet SAE reporting criteria, should be recorded on the AE eCRF; AEs that meet the definition of an SAE should additionally be reported following the procedures noted in Section 14.2.2.

14.3.1. Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient’s own words (verbatim) unless, in the opinion of the investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF). If a diagnosis is subsequently

established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

14.3.2. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the AE eCRF. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF.

14.3.3. Abnormal Laboratory Values

Any Grade 3 or 4 laboratory abnormalities or any clinically significant Grade 1 or 2 laboratory value(s) should be recorded as an AE. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF.

14.3.4. Deaths

For this protocol, observation of the clinical and laboratory AEs produced by study drug is the primary safety endpoint.

Deaths that occur during the protocol-specified AE reporting period that are attributed by the investigator solely to progression of disease will be recorded on the "Trial Discontinuation" eCRF. All other on trial deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the CRO Safety Department.

When recording an SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE report and AE page of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" [not otherwise specified] on the eCRF AE page.

14.3.5. Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE (refer to Section 14.2.1).

14.3.6. Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the trial. Such conditions should be recorded on the General Medical History eCRF. A pre-existing medical condition

should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the trial. When recording such events on an SAE Report Form and/or AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

14.3.7. Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to Section 14.4 for specific instructions.

14.3.8. New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the serious criteria (see Section 14.2.1). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

14.3.9. Lack of Efficacy

When there is deterioration in the condition for which the study treatment is being used, there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the Sponsor or reporting physician considers that the study treatment contributed to the deterioration of the condition, the deterioration should be considered lack of efficacy and not an AE. Disease progression should not be reported as an AE but noted in the Disease Evaluation eCRF.

14.4. Protocol-Defined Events of Special Interest

The following are events of special interest, and will need to be reported expeditiously (see Section 16.1.1):

Pregnancy, Abortion, Birth Defects/Congenital Anomalies:

If a patient or the partner of a male patient becomes pregnant while enrolled in the trial, a Pregnancy Form should be completed and faxed to the CRO Safety Department. The CRO Safety Department should be notified expeditiously, whether or not it meets the criteria for expedited reporting. In addition, the investigator should follow the pregnancy until completion or until pregnancy termination (spontaneous, accidental, or therapeutic abortion) and then notify the CRO Safety Department of the outcome by completing a follow-up Pregnancy Form. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly/birth defect), the investigator should follow the procedures for reporting SAEs.

Other Events of Special interest

Any clinically significant ECG abnormalities should be reported immediately.

Study Drug Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the trial treatment that is symptomatic, even if not fulfilling a

seriousness criterion, is to be reported immediately (within 1 day) using the corresponding screens in the eCRF, and following the same process described for SAE reporting (see Section 14.2.2).

Overdose information for ensartinib is not available.

For additional information on ensartinib, see the IB. For additional information on crizotinib, refer to the prescribing information.

15. STATISTICAL CONSIDERATIONS

15.1. Statistical Design

This is an open-label, randomized, Phase 3 study comparing the efficacy and safety of the ALK inhibitors ensartinib and crizotinib in patients with ALK+ NSCLC. The primary efficacy endpoint will be PFS based upon an independent radiology review.

15.2. Randomization and Stratification

This study will employ a 1:1 randomization. Patients will be stratified based on the following factors:

- Prior chemotherapy: none vs. 1 prior regimen
- Performance Status: 0 or 1 vs. 2
- CNS metastases at baseline: no vs. yes
- Geographic region: Asia vs. rest of the world

Randomization will be conducted centrally via an IVRS using a permuted block randomization. This procedure will ensure balance by treatment arm for the stratification factors of interest.

To ensure sufficient numbers of patients from the rest of the world, enrollment will be capped in the Asiac region to no more than 60% of the planned number of patients.

15.3. Analysis Populations

The definitions of analysis populations are as follows:

1) Enrolled (Intent-to-Treat; ITT) - This population will comprise all patients who were enrolled (randomized) in the study whether or not the study drug was administered. Patients will be assigned to treatment groups based on the randomized drug assignment. This population will be the primary population analyzed for efficacy.
2) Safety - This population will comprise all enrolled patients who receive at least one dose of study drug. Patients will be assigned to treatment groups based on the actual drug received. This population will be analyzed for safety.
3) Modified Intent-to-Treat (mITT) – The mITT Population will comprise all patients with confirmed ALK-positive disease by centrally-performed FDA-approved assay. Patients will be assigned to treatment groups based on the randomized drug assignment. This population will be analyzed for PFS and overall survival.
4) Per Protocol (PP) – The Per Protocol Population will comprise those ITT patients who meet major eligibility criteria affecting efficacy as specified in the Statistical Analysis Plan. This population will be analyzed for PFS and overall survival.

For sensitivity analyses, the efficacy endpoints may be analyzed in the mITT and PP Populations and subsets of the ITT Population. Additional sensitivity analyses will be conducted to assess the impact of the global pandemic on potential missing data.

15.4. Procedures for Handling Missing Data

Besides the specified censoring rules (see Section 15.7), no further imputation for missing data will be applied to the efficacy endpoints

15.5. General Statistical Considerations

Continuous endpoints will be summarized using descriptive statistics, which will include the number of patients with a valid measurement (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages.

Time-to-event endpoints will be analyzed using Kaplan-Meier product limit methods to estimate the survival distribution, median time-to-event with 95% confidence interval, patients at risk, patients with an event, patients censored and survival probabilities at selected time points.

Response to treatment will be assessed by central radiology review and by the investigator based on RECIST v1.1 criteria for systemic and CNS disease.

Time to event endpoints will be analysed using Kaplan-Meier methodology. One month is considered 30.4275 days.

The safety endpoints will be listed and/or summarized by relevant time points, as appropriate.

In general, the baseline value for efficacy and safety variables is the last non-missing value before before the first dose of study treatment. Data listings will be created to support each table and to present all data.

Unless otherwise specified, all statistical tests will be 2-sided and will be carried out at the alpha = 0.05 level of significance. Further details regarding the statistical anlaysis are contained in the following sections and in the Statistical Analysis Plan (SAP).

15.6. Study Population Data

Patient disposition will be summarized for the ITT Population. The total number of patients for each defined analysis population will also be tabulated. The demographic and baseline characteristics will be summarized descriptively for the ITT and Safety Populations. Study treatment exposure and study duration will be summarized using descriptive statistics for the Safety Population.

15.7. Efficacy Analyses

15.7.1. Primary Efficacy Analysis

The primary efficacy endpoint of PFS will be based on IRR using RECIST 1.1 criteria. The primary final analysis will be conducted when 190 PFS per IRR events are reached in the ITT Population. PFS analysis will be based on the log-rank test. A stratified log rank test will be used as supportive evidence of efficacy. The supportive analysis will be stratified by the factors

used for randomization . Kaplan-Meier methods will be used to estimate the PFS survival distribution, and estimates of median PFS will be provided with 95% confidence intervals. Hazard ratio estimates will also be presented using Cox models.

PFS is defined as the time in months from date of randomization to the first date of progression or death due to any cause. The date of progression is the date of a new lesion or the date of radiological measurements of target lesions that meets criteria for progression. Suspected clinical progression should be confirmed by radiologic assessment. Patients who are alive and have not progressed or are lost to follow-up as of a data analysis cutoff date will be rightcensored. Censoring rules will include the following:

- Patients last known to be alive and progression-free will be censored at the date of the last adequate objective disease assessment.
- Patients with no on study disease assessments will be censored at the date of randomization unless death occurred prior to the first planned assessment (in which case the death is an event).
- Patients with inadequate baseline disease assessment will be censored at the date of randomization.
- Patients who received alternate therapy prior to progression will be censored at the date of the last adequate objective assessment prior to receiving alternate therapy.
- Patients with an unacceptably long interval (>16 weeks, i.e., two or more consecutive objective disease assessments were missed) since the last adequate response assessment and who have a PFS event right after the missing assessments are censored at the time of last adequate objective assessment prior to the missing assessments. If only one adequate disease assessment is missing (i.e., interval between adequate assessments is ≤16 weeks) or if patients are still progression-free at the next adequate response assessment following the missing assessment, then subsequent response assessments will be used for PFS determination.

Besides the stratified log-rank test, other sensitivity analyses for PFS will be performed to examine the robustness of the primary analysis, including using other PFS censoring criteria and evaluating censoring patterns by treatment group. PFS will be analysed for the mITT and PP populations as sensitivity analyses. Additonal sensitivity analyses such as global pandemic impact on potential missing data may be specified in the SAP.

One interim analysis is planned after approximately 75% of the total expected PFS events have been observed. An O'Brien-Fleming Lan-DeMets (DeMets and Lan, 1994) alpha spending function will be use to control at 2-sided alpha level of 0.05. The interim will be performed after the first 143 events have been observed and the primary endpoint of PFS will be tested at a 2sided alpha level of 0.019.

15.7.2. Secondary/Exploratory Efficacy Analyses

Secondary efficacy endpoints will be analyzed for the ITT Population. The key secondary efficacy endpoints are:

- Overall survival (OS)
- CNS response rate (as determined by IRR)
- Time to CNS progression (as determined by IRR)
- Objective response rate (ORR; as determined by IRR)

Among key secondary endpoints, only OS will be tested formally at 0.05 if the primary endpoints of PFS is statistically significant. Other secondary endpoints will be tested at 0.05 each and will be considered as exploratory.

OS is defined as the time in months from date of randomization to death due to any cause. Patients who are alive or lost to follow-up as of a data analysis cutoff date will be right-censored. The censoring date will be determined from the patients' date of last contact or data analysis cutoff date, whichever event occurs first.

Two interim analyses of OS will be performed at the time of the interim and final analysis of the primary endpoint of PFS respectively. First interim analysis will be performed when a total of 56 deaths are expected at approximately 75% (143/190) of maturity for PFS events by IRR. Second interim analysis will be performed when a total of 75 deaths are expected at 100% (190/190) of maturity for PFS events by IRR. The OS will be tested at alpha level of 0.0006 for first interim analysis and 0.0037 for second interim respectively, using O'Brien-Fleming LanDeMets alpha spending function at 2-sided alpha level of 0.05. The final analysis for OS will be performed once approximately 145 deaths (50% of 290 subjects enrolled) have died. The median OS in the crizotinib arm is assumed to be 30 months and the expected median OS in the ensartinib treatment arm is 37.5 months, equating to an HR of 0.8. On the basis of the sample size powered for PFS, the trial will not be powered to demonstrate a statistically significant difference in OS of this magnitude.

CNS ORR is defined as the proportion of patients with CNS disease at baseline who have an objective response in CNS lesions (i.e., those who achieve a best response of CR or PR) per CNS RECIST criteria. As supportive analysis, CNS ORR will also be calculated as the proportion of patients with measurable CNS disease at baseline who have an objective response in CNS lesions.

Time to CNS progression is defined as the time in months from date of randomization to the first date of documented CNS progression by RECIST criteria. This includes patients with CNS metastases at baseline as well as those without CNS metastases at baseline but subsequently develop CNS metastases. The same censoring rules for PFS will apply to time to CNS progression except that this will be based only on CNS progression.

ORR is defined as the proportion of patients in ITT who have an objective response (i.e., those who achieve a best response of CR or PR) per RECIST 1.1 criteria. As supportive analysis, ORR

will also be calculated as the proportion of patients with measurable disease who have an objective response.

The analysis for CNS ORR and ORR will be based on CMH test, and for time to CNS progression per IRR and OS will be similar to the primary analysis of PFS.

Other secondary efficacy endpoints are:

- PFS (based on investigator assessment)
- ORR (based on investigator assessment)
- Time to response (based on investigator assessment and IRR)
- Duration of response (based on investigator assessment and IRR)
- CNS Response Rate (based on investigator assessment)
- Time to CNS progression (based on investigator assessment)
- Patient reported time to deterioration (TTD) as measured by the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale
- Patient reported health-related quality of life (HRQoL) as measured by the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale

Exploratory efficacy endpoints include:

- Pharmacodynamic (PD) and possible pharmacogenetic (PG) assessments
- Biomarkers in blood or/and tissue sample

Duration of objective response is defined from the date of the first recorded objective response (CR or PR) to the first date of documented disease progression. The same censoring rules for PFS will apply to duration of objective response.

Duration of disease control is defined from the date of the first recorded response of CR, PR or SD to the first date of documented disease progression. The same censoring rules for PFS will apply to duration of disease control.

Time to response is defined as the time from date of randomization to the date of the first recorded objective response (CR or PR).

The number of patients with a CR, PR, SD, PD and NE by RECIST will be listed and summarized. The number of patients with brain metastases at baseline with a CR, PR, SD, PD, and NE by RECIST criteria will also be listed and summarized.

The EORTC C30/LC13 QoL questionnaire is a health-related quality of life instrument consisting of 13 items for use in lung cancer clinical trials, in which the patient assesses symptoms or problems experienced over the past week. EORTC C30/LC13 items will be summarized by time point. Analysis of time to deterioration (TTD) as measured by the EORTC C30/LC13 will be described in the SAP.

The Lung Cancer Symptom Scale is a QoL assessment designed for use in clinical trials in patients with lung cancer. Patients are asked to assess 6 symptoms and their effect on symptomatic distress, functional activities, and global quality of life on 9 visual analog scales.

Results will be summarized by time point. Analysis of time to deterioration (TTD) will be described in the SAP.

15.7.3. Subgroup Analysis

The primary endpoint of PFS and the key secondary efficacy endpoints of CNS ORR per IRR, time to CNS progression per IRR, ORR per IRR and OS will be also analyzed in subgroups based on stratification variables, as well as demographic and baseline patient characteristics (e.g., age, race, sex), and possibly exploratory biomarkers.

In each defined subgroup, the analysis will be carried out using the same type of methodology as described for the overall analysis of the corresponding endpoint. These results will be considered exploratory because of the multiplicity issue and also smaller sample sizes that cannot be pre-specified. For subgroups without an adequate number of patients, the analysis will not be performed.

15.8. Pharmacodynamics/Biomarkers

Archived or fresh tumor tissue and blood samples will be collected and may be analyzed for exploratory biomarkers to assess correlation with clinical outcomes from study participants. In addition to tissue available at baseline (archival tissue or fresh biopsy), patients will be requested to undergo a post-treatment tumor biopsy upon progression. However, the post-treatment biopsy is optional. In addition, if possible, blood samples will be obtained from as many ensartinib patients as possible for pharmacogenetic analysis in the event that outliers with respect to efficacy, tolerability/safety, or exposure are identified.

No formal statistical analysis of pharmacodynamics endpoints will be performed. Pharmacodynamic data from each assay will be listed and possible relationships between PK and pharmacodynamic variables may be explored. Biomarker data will be summarized using descriptive statistics. The results may be pooled with data from other studies to generate hypotheses to be tested in future studies.

15.9. Pharmacokinetics

Sparse PK sampling for ensartinib patients will be performed in this trial at selected sites. To characterize exposure differences in Asian populations, PK sampling will be required at sites in China. Blood samples will be obtained at trough levels and at the approximate time of C_{max} (see Section 9.7 and Appendix E). Plasma–concentration data from these samples will be analyzed using a PopPK approach using nonlinear mixed effects modeling.

In addition, if appropriate, the sparse PK data may be evaluated with respect to efficacy outcomes and AEs considered to be drug-related to determine if a relationship between these might exist. Gender and age differences in toxicity may also be evaluated. PK data may be examined on an ongoing basis while the study is being conducted.

Details on the plans for the PK analyses will be included in the SAP.

15.10. Safety Analyses

The analyses of safety will be performed on the Safety Population. Safety data will be examined on an ongoing basis while the study is being conducted.

Terminology from version 16.0 of the Medical Dictionary for Drug Regulatory Activities (MedDRA) will be used initially to assign System Organ Class (SOC) and Preferred Terms classification to AEs and diseases, based on the original terms entered on the eCRF. MedDRA version may be updated throughout the project.

The incidence of treatment-emergent AEs (TEAEs) will be summarized by SOC, Preferred Terms, relationship to the study treatment, and severity. A by-patient listing will be provided for those patients who experience an SAE, including death, or experience an AE associated with early withdrawal from the study or study treatment.

15.10.1. Analysis of Treatment-emergent Adverse Events

TEAEs are AEs that occur, having been absent before the first dose of study treatment, or have worsened in severity after initiating the study treatment. TEAEs will be coded using MedDRA and assigned grades based on version 4.03 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).

The number and percentage of patients reporting TEAEs and TEAEs considered related to study drug by the investigator will be tabulated by the worst CTCAE grade, system organ class, and preferred term, with an emphasis on Grade 3 and Grade 4 AEs. Similarly, the number and percentage of patients reporting treatment-emergent SAEs and drug-related SAEs will be tabulated, as well as TEAEs leading to discontinuation of study treatment.

A by-patient AE (including treatment-emergent) data listing including, but not limited to, verbatim term, preferred term, system organ class, CTCAE grade, and relationship to study treatment will be provided. Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study treatments, will be listed.

15.10.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation for the Safety Population, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be summarized for the maximum and minimum posttreatment values and the values at the End of Treatment visit.

Abnormal clinical laboratory results will be graded according to NCI CTCAE version 4.03, if applicable, and the grade will be presented in a by-patient data listing. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI CTCAE grade, will be provided for clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

Incidence rates of grade 3 or 4 ALT elevations are of particular interest and will be compared by treatment group using a Fisher's exact test.

15.10.3. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation for the Safety Population, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In

addition, mean change from baseline will be presented for the maximum and minimum posttreatment values and the values at the End of Treatment visit.

15.10.4. Electrocardiogram Analyses

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation for the Safety Population, as well as for the change from baseline, based on the readings provided by ERT. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, the number and percentage of patients with ECG interval values meeting certain criteria will be tabulated (e.g., QTcF ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms) and QTcF maximum changes from baseline (>30 ms and >60 ms) over all post treatment evaluations will be summarized. ECG data will also be presented in the data listings.

15.10.5 Power and Sample Size Determination

This study will enroll up to 316 ITT patients, using a 1:1 randomization. A sample size of 266 will allow detection of a hazard ratio of 0.625, with 90% power and a 2-sided alpha of 0.05 in the ITT population. This estimate assumes a median PFS of 10 months in the crizotinib arm (based on the assumption that approximately 2/3 of patients will be chemotherapy-naïve), with an improvement to 16 months in the ensartinib arm, and 27 month accrual period with 12 months of additional follow-up. The final analysis will be performed after 190 PFS events have been observed in the ITT population. An interim analysis will be performed after approximately 75% of the planned PFS events per IRR have occurred (approximately 143 of 190 total events).

15.11. Data and Safety Monitoring Board

The trial will utilize the services of a Data Monitoring Committe (DMC) to monitor patient safety and review the results of the interim analysis. Details will be provided in the DMC charter.

15.12. Steering Committee

The trial will utilize a Steering Committee to provide input on any changes to the study, consider recommendations from the DMC, and supervise the progress of the study.

16. DISCONTUATION FROM TRIAL TREATMENT

Patients will be discontinued from trial treatment for any of the following reasons:

- Disease progression. Note that if a patient is determined to have progressive disease but is clinically doing well and the investigator feels it is in the patient's best interest to remain on study treatment, the patient may be allowed to continue after discussion with the Medical Monitor.
- Intolerable drug-related toxicity (includes most instances of Grade 4 nonhematologic toxicity; Grade 3 non-hematologic toxicity lasting >7 days; Grade 3 non-hematologic toxicity not expected to be manageable and reversible with dose reduction; patients who require a treatment delay of more than 4 weeks due to treatment-related toxicity; elevated ALT or AST ≥3x ULN in conjunction with bilirubin ≥1.5x ULN (for crizotinib) or with bilirubin ≥2x ULN (for ensartinib) (in absence of cholestasis or

hemolysis) and no correctable, non-drug related cause; pneumonitis of any grade not attributable to NSCLC progression, other pulmonary disease, infection, or radiation effect; QTcF >500 ms or ≥60 ms change from baseline with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia; bradycardia with life-threatening consequences where urgent intervention is indicated [see Section 7.3.2])

- Patient requests to discontinue treatment/withdraw from the trial (withdrawal of consent)
- Pregnancy (see Section 16.1.1.)
- Inability or unwillingness of the patient to comply with trial requirements
- Condition requiring therapeutic intervention not permitted by the protocol
- Investigator assessment that it is in patient's best interest to discontinue therapy (e.g., intercurrent illness). If necessary, treatment can be held at the investigator's discretion, but the sites should make every effort to discuss with sponsor medical monitor before permanently discontinuing therapy.
- Lost to follow-up
- Discontinuation of the study by the Sponsor

In the event of a patient's withdrawal, the investigator will promptly notify the Medical Monitor and will make every effort to complete the end-of-study assessments. After withdrawal from protocol treatment, patients must be followed for AEs for 30 calendar days after their last dose of trial drug. All previously reported AEs must be followed or new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for this decision in the patients' medical records and as a comment on the eCRF.

All patients who have CTCAE Grade 3 or 4 laboratory abnormalities at the time of withdrawal must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the eCRF.

16.1.1. Pregnancy

During the course of the trial, all women of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix B) must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator).

If an investigator suspects that a patient may be pregnant prior to administration of trial drug, the trial drug must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any trial drug, and must be discontinued from the trial.

If an investigator suspects that a patient may be pregnant after the patient has been receiving trial drug, the trial drug must immediately be withheld until the result of the pregnancy test is

confirmed. If a pregnancy is confirmed, the trial drug must be immediately and permanently stopped, the patient must be discontinued from the trial, and the investigator must notify the Medical Monitor as soon as possible. Note, however, that if the patient decides that the pregnancy will be terminated, the patient may be allowed to remain in the study, if appropriate. This also needs to be discussed with the Medical Monitor. If a patient becomes pregnant while enrolled in the trial, or the partner of a male patient becomes pregnant, a Pregnancy Form should be completed and faxed to the CRO Safety Department. For more details regarding handling and reporting of pregnancies that occur during treatment, see Section 12.4.

17. EARLY TERMINATION OF STUDY

The study may be terminated at any time by the Sponsor, such as in the event of unacceptable toxicity or new information that significantly impacts patient safety or the impossibility to guarantee study conduct per protocol or patients' safety in case of unforeseen circumstances (i.e. a pandemic as the COVID-19). In the event that the study is discontinued, the Sponsor shall immediately inform all of the investigators and appropriate regulatory authorities. The trial may also be terminated at a study site if the investigator does not adhere to the protocol.

18. CLINICAL MONITORING

18.1. Site Monitoring Plan

Site monitoring shall be conducted to ensure the human subject protection, trial procedures, laboratory, trial intervention administration, and data collection processes are of high quality and meet Sponsor, ICH/GCP and, when appropriate, regulatory guidelines. The Site Monitoring Plan shall define aspects of the monitoring process.

19. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This trial will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and FDA CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

19.1. IRB/IEC Approval

The trial protocol, informed consent form (ICF), IB, available safety information, patient documents (e.g., trial diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., PI payments) and compensation available to the patients and documentation evidencing the PI's qualifications should be submitted to the IRB/IEC for ethical review and approval if required by local regulations, prior to the trial start.

The PI/Sponsor/CRO and/or designee will follow all necessary regulations to ensure appropriate initial and ongoing IRB/IEC trial review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the ICF. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB/IEC.

Safety updates for ensartinib will be prepared by the Sponsor or its representative, as required, for submission to the relevant IRB/IEC.

19.2. Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to trial initiation. If required, the Sponsor (or its representative) will also ensure that the implementation of substantial amendments to the protocol and other relevant trial documents happen only after approval by the relevant regulatory authorities.

Safety updates for ensartinib will be prepared by the Sponsor or its representative, as required, for submission to the relevant regulatory authority.

19.3. Insurance and Indemnity

Details of insurance and/or indemnity will be contained within the written agreement between the PI or site and the Sponsor.

19.4. Informed Consent

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated ICF.

The ICF will be submitted for approval to the IRB/IEC that is responsible for review and approval of the trial. Each consent form must include all of the relevant elements currently required by the FDA and EU regulations, as well as local/country-specific regulations.

Before recruitment and enrollment into the trial, each prospective candidate will be given a full explanation of the trial. Once the essential information has been provided to the prospective candidate, and the investigator is sure that the individual candidate understands the implications of participating in this trial, the candidate will be asked to give consent to participate in the trial by signing an ICF. A notation that written informed consent has been obtained will be made in the patient’s medical record. A copy of the ICF, to include the patient’s signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the trial design or the potential risks to the patients, the patient’s consent to continue participation in the trial should be obtained.

During unsual circumstances, e.g. global pandemics, alternative processes to consent may be used, for example, the consent form may be sent to the subject or the subject’s legally authorized representative by facsimile or e-mail, and the consent interview may then be conducted by telephone when the subject or subject’s legally authorized representative can read the consent form during the discussion. There may be other adequate alternatives, however, the patient should also be reconcented once able to visit the investigative site. Alternate consenting processes, should be approved by overseeing ethics committees.

19.5. Confidentiality

19.5.1. Patient Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

No patient names will be supplied to the Sponsor. In order to maintain confidentiality, patients will be identified by site number and patient number. This information will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF or database. No material bearing a patient's name will be kept on file by the Sponsor. Patients will be informed of their rights within the ICF.

In compliance with ICH GCP guidelines, FDA regulations, and in accordance with local data protection laws, it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities, and the IRB/IEC direct access to review the patient's original medical records at the site for verification of trial-related procedures and data.

In the event that a patient revokes authorization to collect or use his or her personal health information (PHI), the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled trial period.

If the results of the study are published, the patient's identity will remain confidential. The investigator will maintain a list to enable patients' records to be identified.

19.5.2. Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the CRO database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub-investigator, the CRO shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

19.6. Financial Information

The finances for this trial will be subject to a separate written agreement between the Sponsor and applicable parties. Any investigator financial disclosures as applicable to 21CFR Part 54 and local regulatory requirements shall be appropriately provided.

20. RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

20.1. Amendments to the Protocol

Amendments to the protocol shall be planned, documented and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by the Sponsor (or its representative). All amendments require review and approval of the

Sponsor and the PI supporting the trial. The written amendment must be submitted to the appropriate IRB(s)/IEC(s) for the board's approval.

Items requiring a protocol amendment with IRB/IEC approval and FDA approval or notification include, but are not limited to, the following:

- Change to trial design
- Risk to patient
- Increase in dose or patient exposure to drug
- Subject number increase
- Addition or removal of tests and / or procedures
- Addition/removal of an investigator

It should be noted that if an amendment to the protocol substantially alters the trial design or the potential risks to the patients, their consent to continue participation in the trial should be obtained.

20.2. Documentation Required to Initiate Trial

Before the trial may begin, documentation required by ICH GCP, FDA, and/or local regulatory authorities must be provided by the investigator. The required documentation will be requested by and should be submitted to the CRO.

20.3. Trial Documentation and Storage

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated trial duties and should ensure that all persons assisting in the conduct of the trial are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation.

Source documents are the original documents, data, records and certified copies of original records of clinical findings, observations and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG tracings, copies or transcriptions certified after verification as being accurate and complete, photographs, microfilm or magnetic media, X-rays or other radiographs, and correspondence.

The PI and trial staff are responsible for maintaining a comprehensive and centralised filing system (Site Trial File/SSF or Investigator Site File/ISF) of all trial-related (essential) documentation, suitable for inspection at any time by the Sponsor (or its representatives) and/or applicable regulatory authorities. The ISF/SSF must consist of those documents that individually or collectively permit evaluation of the conduct of the trial and the quality of the data produced. The ISF/SSF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, or applical local regulations, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB/IEC approval documents, Financial Disclosure forms, patient

identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the trial drug, including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

The Sponsor shall maintain adequate investigational product records and financial interest records as per 21 CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by the FDA; or, in the event that the marketing application has not been approved by the FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use is discontinued and the FDA has been notified of the discontinuation, or as required by other regulatory country requirements.

The IRB/IEC shall maintain adequate documentation/records of IRB/IEC activities for at least 3 years after completion of the research in accordance with local regulations.

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including, but not limited to, those defined by GCP as essential (this includes supporting documentation and administrative records), for the longer of: (a) 2 years after the last marketing authorization for the study drug has been approved or the sponsor has discontinued its research with respect to such drug or (b) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the sponsor in writing of its intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

Study documents may not be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed upon designee, such as the Medical Monitor, another Investigator, or the institution where the study was conducted.

20.4. Data Collection

The trial eCRF is the primary data collection instrument for the trial. eCRFs will be completed using the English language and should be kept current to enable the monitor to review the patients' status throughout the course of the trial.

In order to maintain confidentiality, patients will be identified by site number and patient number in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the CRO and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested on the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown". For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the PI, once all data for that patient is final.

20.5. Trial Monitoring, Auditing, and Inspecting

The investigator will permit trial-related monitoring, quality audits, and inspections by the government regulatory authorities, and the Sponsor or its representative(s) of all trial-related documents (e.g., source documents, regulatory documents, data collection instruments, eCRFs).

The investigator will ensure the capability for inspections of applicable trial-related facilities. The investigator will ensure that the trial monitor or any other compliance or quality assurance (QA) reviewer is given access to all trial-related documents and trial-related facilities.

Participation as an investigator in this trial implies the acceptance of potential inspection by government regulatory authorities and the Sponsor or its representative(s).

At the Sponsor's discretion, Source Document Verification (SDV) may be performed on all data items or a percentage thereof. During unusual circumstances, e.g. global pandemics, alternatives to onsite source document verification or data reviews may be used if local regulations/ethics committees allow, such as remote monitoring.

20.6. Quality Assurance and Quality Control

An Auditing Plan document separate from the protocol will be developed to establish the criteria by which independent auditing shall be conducted during the conduct of the trial to assess compliance with GCP and applicable regulatory requirements. Data or documentation audited shall be assessed for compliance to the protocol, accuracy in relation to source documents and compliance to applicable regulations.

Each trial site shall be required to have Standard Operating Procedures (SOPs) to define and ensure quality assurance/control processes for trial conduct, data generation and collection, recording of data/documentation and reporting according to the protocol, GCP and any applicable local, national or international regulations.

20.7. Disclosure and Publication Policy

[redacted]

[redacted]

21. REFERENCES

Acquaviva et al. 2008

Acquaviva J, Wong R, Charest A. The multifaceted roles of the receptor tyrosine kinase ROS in development and cancer. Pathol Int. 2008; 58:226-32.

ALECENSA® (alectinib) PI 2017
U.S. Prescribing Information for ALECENSA® (alectinib) – November 2017.

ALUNBRIG® (brigatinib) PI 2017 U.S. Prescribing Information for ALUNBRIG® (brigatinib) – October 2017

Bang et al. 2008

Bang Y, Kwak,, E.L., Shaw, A.T., Camidge, D.R., Iafrate, A.J., Maki, R.G., Solomon, B.J., Ou, S.I., Salgia, R., Clark, J.W. Clinical activity of the oral ALK inhibitor PF-02341066 in ALKpositive patients with non-small cell lung cancer (NSCLC). J Clin Oncol 2010; 28: suppl; abstract 3.

Chen et al 2008

Chen Y, Takita J, Choi YL, et al. Oncogenic mutations of ALK kinase in neuroblastoma. Nature 2008; 455: 971-4.

Choi et al. 2008

Choi YL, Takeuchi K, Soda M, et al. Identification of novel isoforms of the EML4-ALK transforming gene in non-small cell lung cancer. Cancer Res 2008; 68: 4971-6.

DeMets et al. 1994

DeMets DL, Lan KK. Interim analysis: The alpha spending function approach. Stat Med. 1994 Jul 15-30;13(13-14):1341-52.

George et al 2008

George RE, Sanda T, Hanna M, et al. Activating mutations in ALK provide a therapeutic target in neuroblastoma. Nature 2008; 455: 975-8.

Hanna et al. 2004

Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004; 22: 1589-97.

Horn and Pao. 2009

Horn L, Pao W. EML4-ALK: honing in on a new target in non-small-cell lung cancer. J Clin Oncol 2009; 27: 4232-5.

Janoueix-Leorosey et al. 2008

Janoueix-Lerosey I, Lequin D, Brugieres L, et al. Somatic and germline activating mutations of the ALK kinase receptor in neuroblastoma. Nature 2008; 455: 967-70.

Koivunen et al. 2008

Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res 2008; 14: 4275-83.

Kwak et al. 2010

Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-smallcell lung cancer. N Engl J Med 363:1693-1703.

Lawrence et al. 2000

Lawrence B, Perez-Atayde A, Hibbard MK, et al. TPM3-ALK and TPM4-ALK oncogenes in inflammatory myofibroblastic tumors. Am J Pathol 2000; 157: 377-84.

Lovly et al. 2011

Lovly CM, Heuckmann JM, de Stanchina E, Chen H, Thomas RK, Liang C, Pao W. Insights into ALK-driven cancers revealed through development of novel ALK tyrosine kinase inhibitors. Cancer Res 2011; 71:4920-31.

Median Technologies. 2018

Imaging Review Charter; Protocol X396-CLI-301, Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients

Mok et al. 2014

Mok T, Kim D-W, Wu Y-L, et al. First-line crizotinib versus pemetrexed-cisplatin or pemetrexed-carboplatin in patients (pts) with advanced ALK-positive non-squamous non-small cell lung cancer (NSCLC): results of' a phase IlI study (PROFILE 1014). J Clin Oncol 2014; 32:15s (suppl; abstr 8002).

Morris et al. 1994

Morris SW, Kirstein MN, Valentine MB, et al. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. Science 1994; 263: 1281-4.

Mosse et al. 2008

Mosse YP, Laudenslager M, Longo L, et al. Identification of ALK as a major familial neuroblastoma predisposition gene. Nature 2008; 455: 930-5.

O'Bryan et al. 1991

O'Bryan P, Frye R A, Cogswell P C, Neubauer A et al. xl, a transforming gene isolated from primary human myeloid leukemia cells, encodes a novel receptor tyrosine kinase. Mol Cell Biol. 1991; 11: 5016–5031.

Rikova et al. 2007

Rikova K, Guo A, Zeng Q, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 2007; 131: 1190-203.

Sabbatini et al. 2009

Sabbatini P, Korenchuk S, Rowand JL, et al. GSK1838705A inhibits the insulinlike growth factor-1 receptor and anaplastic lymphoma kinase and shows antitumor activity in experimental models of human cancers. Mol Cancer Ther 2009; 8: 2811-20.

Soda et al. 2007

Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007; 448: 561-6.

Takeuchi et al. 2008

Takeuchi K, Choi YL, Soda M, et al. Multiplex reverse transcription-PCR screening for EML4ALK fusion transcripts. Clin Cancer Res 2008; 14: 6618-24.

Takeuchi et al. 2009

Takeuchi K, Choi YL, Togashi Y, et al. KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. Clin Cancer Res 2009; 15: 3143-9.

Tandon et al. 2011

Tandon M, Vemulla SM and Mittal SK. Emerging strategies for EphA2 receptor targeting for cancer therapeutics .Exp Opinion Ther Targets 2011; 15:31-51.

Weickhardt et al. 2012

Weickhardt AJ, Rothman MS, Salian-Mehta S, Kiseljak-Vassiliades K, Oton AB, Doebele RC, et al. Rapid-onset hypogonadism secondary to crizotinib use in men with metastatic nonsmall cell lung cancer. Cancer. 2012;118(21):5302-9.

Wong et al. 2009

Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009; 115: 1723-33.

XALKORI® (crizotinib) PI 2017

U.S. Prescribing Information for XALKORI® (crizotinib) – July 2017.

Yap et al. 2010

Yap TA and. de Bono JS. Targeting the HGF/c-Met axis: state of play. Mol Cancer Ther 2010; 9:2778.

Zou et al. 2007

Zou HY, Li Q, Lee JH, et al. An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. Cancer Res 2007; 67: 4408-17.

ZYKADIA® (ceritinib) PI 2017

U.S. Prescribing Information for ZYKADIA® (ceritinib) – November 2017.

22. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B: Contraceptive Guidelines

Women of Childbearing Potential are Defined as Follows:

- Any female who has experienced menarche and does not meet the criteria for "Women Not of Childbearing Potential".

Women Not of Childbearing Potential are Defined as Follows:

- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
- Women who are >45 years of age, not using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L)
- Women who are >45 years of age, using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone replacement therapy

Acceptable Contraception Methods:

Male patients with female partners of child-bearing potential and women patients of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the trial and for 90 days following discontinuation of study drug. Male patients must also refrain from donating sperm for 90 days following discontinuation of study drug.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Appendix B: Contraceptive Guidelines (continued)

The following are acceptable forms of secondary contraception, when used with a barrier method and spermicide:

- True abstinence. When this is in line with the preferred and usual lifestyle of the subject. Note that periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to the study drug, and withdrawal are **not** acceptable methods of contraception
- Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- Placement of an intrauterine device (IUD) or intrauterine system (IUS), with the exception of IUD progesterone T
- Established use of oral, injected or implanted hormonal methods of contraception Tubal ligation

The following are **unacceptable** forms of contraception for women of childbearing potential:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Appendix C: Drugs That Can Cause QT Prolongation with Known Risk or Possible Risk of Torsades de Pointes

The following is taken from https://crediblemeds.org/ (13 Dec 2017). This may not be a comprehensive list. For more details and periodic updates, see https://crediblemeds.org/.

Alfuzosin (Uroxatral®)[2]
Amiodarone (Cordarone® and others)[1]
Anagrelide (Agryline® and others)[1]
Apomorphine (Apokyn® and others)[2]
Aripiprazole (Abilify® and others)[2]
Arsenic trioxide (Trisenox®)[1]
Artenimol + Piperaquine (Eurartesim®)[2]
Asenapine (Saphris® and others)[2]
Astemizole (Hismanal®)[1]
Atomoxetine (Strattera®)[2]
Azithromycin (Zithromax® and others)[1]
Bedaquiline (Sirturo®)[2]
Bendamustine (Treanda® and others)[2]
Benperidol (Anquil® and others)[2]
Bepridil (Vascor®)[1]
Betrixaban (Bevyxxa®)[2]
Bortezomib (Velcade® and others)[2]
Bosutinib (Bosulif®)[2]
Buprenorphine (Butrans® and others)[2]
Cabozantinib (Cometriq®)[2]
Capecitabine (Xeloda®)[2]
Ceritinib (Zykadia®)[2]
Chloroquine (Aralen®)[1]
Chlorpromazine (Thorazine® and others)[1]
Cilostazol (Pletal®)[1]
Ciprofloxacin (Cipro® and others)[1]
Cisapride (Propulsid®)[1]
Citalopram (Celexa® and others)[1]
Clarithromycin (Biaxin® and others)[1]
Clofazimine (Lamprene®)[2]
Clomipramine (Anafranil™)[2]
Clozapine (Clozaril® and others)[2]
Cocaine (Cocaine)[1]
Crizotinib (Xalkori®)[2]
Cyamemazine (cyamepromazine) (Tercian)[2]
Dabrafenib (Tafinlar®)[2]
Dasatinib (Sprycel®)[2]
Degarelix (Firmagon®)[2]
Delamanid (Deltyba)[2]
Desipramine (Pertofrane and others)[2]
Deutetrabenazine (Austedo™)[2]
Dexmedetomidine (Precedex and others)[2]
Disopyramide (Norpace®)[1]
Dofetilide (Tikosyn®)[1]
Dolasetron (Anzemet)[2]
Domperidone (Motilium® and others)[1]
Donepezil (Aricept®)[1]
Dronedarone (Multaq®)[1]
Droperidol (Inapsine® and others)[1]
Efavirenz (Sustiva® and others)[2]
Eliglustat (Cerdelga®)[2]
Epirubicin (Ellence® and others)[2]
Eribulin mesylate (Halaven®)[2]
Erythromycin (E.E.S.® and others)[1]
Escitalopram (Cipralex® and others)[1]
Ezogabine (Retigabine) (Potiga and others)[2]
Felbamate (Felbatol)[2]
Fingolimod (Gilenya®)[2]
Flecainide (Tambocor® and others)[1]
Fluconazole (Diflucan® and others)[1]
Flupentixol (Depixol and others)[2]
Gatifloxacin (Tequin®)[1]
Gemifloxacin (Factive®)[2]
Granisetron (Kytril and others)[2]
Grepafloxacin (Raxar®)[1]
Halofantrine (Halfan®)[1]

Haloperidol (Haldol® (US & UK) and others)[1]
Hydrocodone- ER (Hysingla™ ER and others)[2]
Ibogaine[1]
Ibutilide (Corvert®)[1]
Iloperidone (Fanapt® and others)[2]
Imipramine (melipramine) (Tofranil™)[2]
Inotuzumab ozogamicin (Besponsa®)[2]
Isradipine (Dynacirc®)[2]
Ketanserin (Sufrexal®)[2]
Lapatinib (Tykerb® and others)[2]
Lenvatinib (Lenvima®)[2]
Leuprolide (Lupron® and others)[2]
Levofloxacin (Levaquin® and others)[1]
Levomepromazine (Nosinan and others)[1]
Levomethadyl (Orlaam®)[1]
Levosulpiride (Lesuride and others)[1]
Lithium (Eskalith and others)[2]
Melperone (Bunil and others)[2]
Mesoridazine (Serentil®)[1]
Methadone (Dolophine® and others)[1]
Midostaurin (Rydapt®)[2]
Mifepristone (Korlym® and others)[2]
Mirabegron (Myrbetriq®)[2]
Mirtazapine (Remeron®)[2]
Moexipril/HCTZ (Uniretic® and others)[2]
Moxifloxacin (Avelox® and others)[1]
Necitumumab (Portrazza®)[2]
Nicardipine (Cardene®)[2]
Nilotinib (Tasigna®)[2]
Norfloxacin (Noroxin and others)[2]
Nortriptyline (Pamelor and others)[2]
Nusinersen (Spinraza®)[2]
Ofloxacin (Floxin®)[2]
Ondansetron (Zofran® and others)[1]
Osimertinib (Tagrisso®)[2]
Oxaliplatin(Eloxatin®)[1]
Oxytocin (Pitocin and others)[2]
Paliperidone (Invega® and others)[2]
Palonosetron (Aloxi®)[2]
Panobinostat (Farydak®)[2]
Papaverine HCl (Intra-coronary)[1]
Pasireotide (Signifor®)[2]
Pazopanib (Votrient®)[2]
Pentamidine (Pentam®)[1]
Perflutren lipid microspheres (Definity®)[2]
Perphenazine (Trilafon and others)[2]
Pilsicainide (Sunrythm)[2]
Pimavanserin (Nuplazid®)[2]
Pimozide (Orap®)[1]
Pipamperone (Dipiperon (EU) and others[2]
Probucol (Lorelco®)[1]
Procainamide (Pronestyl® and others)[1]
Promethazine (Phenergan®)[2]
Propofol (Diprivan® and others)[1]
Prothipendyl (Dominal® and others)[2]
Quinidine (Quinaglute® and others)[1]
Ribociclib (Kisqali®)[2]
Rilpivirine (Edurant® and others)[2]
Risperidone (Risperdal®)[2]
Romidepsin (Istodax®)[2]
Roxithromycin (Rulide® and others)[1]
Saquinavir (Invirase® (combo))[2]
Sertindole (Serdolect® and others)[2]
Sevoflurane (Ulane® and others)[1]
Sorafenib (Nexavar)[2]
Sotalol (Betapace® and others)[1]
Sparfloxacin (Zagam®)[1]
Sulpiride (Dogmatil® and others)[1]
Sultopride (Barnetil and others)[1]
Sunitinib (Sutent®)[2]
Tacrolimus (Prograf® and others)[2]
Tamoxifen (Nolvadex (discontinued 6/13) and others)[2]
Telavancin (Vibativ®)[2]
Telithromycin (Ketek®)[2]

Terfenadine (Seldane®)[1]
Terlipressin (Teripress and others)[1]
Terodiline (Micturin® and others)[1]
Tetrabenazine (Nitoman® and others[2]
Thioridazine (Mellaril® and others)[1]
Tiapride (Tiapridal and others)[2]
Tipiracil and Trifluridine (Lonsurf®)[2]
Tizanidine (Zanaflex® and others)[2]
Tolterodine (Detrol® and others)[2]
Toremifene (Fareston®)[2]
Trimipramine (Surmontil® and others)[2]
Tropisetron (Navoban® and others)[2]
Valbenazine (Ingrezza®)[2]
Vandetanib (Caprelsa®)[1]
Vardenafil (Levitra®)[2]
Vemurafenib (Zelboraf®)[2]
Venlafaxine (Effexor® and others)[2]
Vorinostat (Zolinza®)[2]
Zolepine (Losizopilon® and others)[2]

[1] Drugs with known risk of Torsades de Pointes

[1] Drugs with possible risk of Torsades de Pointes

Appendix D: New York Heart Association (NYHA) Classifications of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix E: Schedule of Assessments for Protocol X396-CLI-301

Procedures	Pre-Treatment	TRIAL TREATMENT						End of Trial Treatment[r]	30 Days Post End of Treatment and Survival
	Screening/ Baseline	Cycle 1 Cycle = approx. 28 days	Cycle 1	Cycle 2	Cycle 3 Through Cycle 18		Cycle 19 Through End of Treatment		
		Day 1 (pre-dose)	Day 15	Day 1[t]	Day 1 (Every 4 Weeks)[t]	Every 2 Cycles (Every 8 Weeks)[t]	Every 3 Cycles (Every12 Weeks)[t]		
TESTS & OBSERVATIONS									
Informed Consent[a]	X[a]								
Medical history (including smoking history)	X								
Physical examination, including whole body skin exam, neuro exam for patients with CNS disease, vital signs, height, weight[c]	X	X[b]	X	X	X		X	X	
ECOG Performance Status	X	X[b]	X	X	X		X	X	
EORTC C30/LC13 QoL questionnaire & LCSS	X	X[b]		X		X[u]	X[u]	X	
Adverse event evaluation	X	X	X	X	X		X	X	X[r]
Concomitant medication review	X	X	X	X	X		X	X	X[r]
LABORATORY TESTS									
CBC, including differential and platelets[d]	X	X[b]	X[d]	X[d]	X		X	X	
Clinical chemistry[e]	X	X[b]	X[e]	X (and at Cycle 2 Day 15)[e]	X		X	X	
Coagulation tests[f]	X	X[b]		X		X	X	X	
Total testosterone		X		X	X[g]			X	
HBsAg, HBeAg, HB viral DNA[v]	X[v]								
12-lead ECG[h]	X	X		X		X	X	X	
Urinalysis[i]	X	X[b]		X				X	
Serum or urine pregnancy test[j]	X			X[w]	X[w]		X[w]	X	X[w]
PK blood[k]		X		X	X (Cycle 3 only)			X	

Study Drug: X-396 (Ensartinib),
Date of Original Protocol: 28 September 2015

Biomarker blood sample collection[s]		X		X	X		X	X	
PG blood sample[l]	X[l]								
Tumor tissue sample[p]	X							X[p]	
DISEASE ASSESSMENT[y]									
CT scan of the chest, abdomen, pelvis[m,q]	X					X	X	X	
MRI of the brain[n,q]	X					X	X	X	
Bone scan[o]	X								
Follow-up for survival									X[x]

Appendix E: Schedule of Assessments for Protocol X396-CLI-301 (continued)

a. Informed Consent must be obtained ≤28 days prior to the initiation of trial treatment.

b. The screening physical examination, ECOG performance status, QoL questionnaires, hematology, blood chemistry, coagulation, and urinalysis tests should be done ≤28 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1, they do not have to be repeated. If these must be repeated for Cycle 1 Day 1, they can be completed ≤ 3 days prior to Cycle 1 Day 1.

c. Physical examinations will include measurements of weight and vital signs (resting heart rate, blood pressure, respiratory rate, temperature). Physical examinations will also include a whole body skin examination in all patients and a neurologic exam for patients with CNS metastases at baseline (document clinically significant findings as for any other clinically significant findings from physical exam) and will be done on Day 1 of each cycle. Note that patients who develop a skin rash thought to be related to study drug, are encouraged to have a skin biopsy and digital photos obtained for evaluation. Note, also, that vital signs should be assessed before blood collection. At the screening visit only, height will also be recorded.

d. Hematology parameters include the following laboratory tests: complete blood cell count with 3-part differential (i.e., total neutrophil count including bands, lymphocytes, monocytes), hemoglobin, hematocrit and platelets. Note: Where required (e.g., **Czech Republic and Germany**, this should be repeated weekly during Cycle 1 and on Cycle 2 Days 1 and 15).

e. Blood chemistry must include glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, albumin, phosphorus, uric acid. This should also be repeated on C2 Day 15, then every cycle and as clinically indicated (e.g. more frequent for level 2, 3 or 4 increases of ALT, AST or bilirubin). In addition, where required, this should be obtained more frequently during the first 2 cycles, (e.g., weekly in the **U.K. and Germany)**. f. Coagulation tests include PT, PTT, INR.

g. Total testosterone will be collected from male patients prior to dosing at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and at the end of trial treatment.

h. Three 12-lead ECGs will be collected approximately 5 minutes apart at the screening visit. On Cycle 1 Day 1, three ECGs will be collected approximately 5 minutes apart pre-dose. Thereafter, three sequential (approximately 5 minutes apart) pre-dose 12-lead ECGs will be collected on the Cycle 2 Day 1 and Cycle 3 Day 1 visits, and then approximately every 8 weeks (increasing to every 12 weeks, +/- 1 week, at Cycle 19 due to impact of COVID-19 pandemic), and at the end of trial treatment visit. In addition, for patients randomized to ensartinib, ECGs will be obtained on Cycle 1 Day 1 and Cycle 2 Day 1 approximately 4 hours (± 1 hour) after dosing regardless of food/fasting. Note that ECGs should be obtained before blood collection.

i. A urine dipstick (pH, specific gravity, blood, protein, glucose) will be done at screening/baseline, Cycle 2 Day 1, and the end of trial treatment visit.

j. A serum or urine pregnancy test will be performed within 1 week prior to initial treatment, if a menstrual cycle is missed during treatment or pregnancy is otherwise suspected, and at the end of treatment visit only for women of childbearing potential.

k. PK blood samples will be collected from ensartinib patients at participating sites. To characterize differences in Asian populations, PK sampling will be required at sites in China for ensartinib patients. Samples will be collected at pre-dose and approximately 4 hours (± 1 hour) after dosing on Cycle 1 Day 1 and Cycle 2 Day 1, whether ensartinib was taken with or without food, pre-dose on Cycle 3 Day 1, and at the end of trial treatment visit if the patient had taken the last dose of study drug the day before the end of trial treatment visit.

l. One pharmacogenetic blood sample (one EDTA tube) will be collected at baseline from as many ensartinib patients as possible for possible future testing. The baseline sample must necessarily have been completed after randomization to ensartinib. As a result, the sample may be pulled on Cycle 1 Day 1, however, it must be prior to dosing.

m. Patient will have CT scan at screening/baseline (≤28 days prior to initiation of treatment), approximately every 8 weeks (increasing to every 12 weeks, +/- 1 week, at Cycle 19 due to impact of COVID-19 pandemic), whenever disease progression is suspected, and at end/withdrawal from study. For patients who discontinue treatment without radiographic progression per RECIST 1.1 (e.g., in patients who discontinue treatment for clinical progression or adverse reactions), disease assessments should continue approximately every 8 weeks after study treatment until radiographic disease progression or alternate therapy is given. (Note: MRI may be used as an alternative to abdomen and pelvis CT scans; the modality used at screening/baseline should be identical at each disease assessment).

n. Gadolinium-enhanced, T1-weighted MRI of brain required for all patients (unless there is a contraindication for MRI, in which case CT with and without contrast may be used). Screening/baseline scans should be performed ≤28 days prior to initiation of treatment and approximately every 8 weeks (increasing to every 12 weeks, +/- 1 week, at Cycle 19 due to impact of COVID-19 pandemic), whenever disease progression is suspected, and at the end/withdrawal from study. For patients who discontinue treatment without radiographic progression (e.g., in patients who discontinue treatment for clinical progression or adverse reactions), disease assessments should continue approximately every 8 weeks (increasing to every 12 weeks, +/- 1 week, at Cycle 19 due to impact of COVID-19 pandemic) after study treatment until radiographic disease progression or alternate therapy is given.

o. Bone scan should be obtained in all patients at screening/baseline (≤28 days prior to initiation of treatment) and repeated during the study if patients become symptomatic or if needed to confirm CR. Note: PET scan may be used as an alternative to bone scan, but must be performed at screening and subsequent scans for consistency.

p. Adequate archival tissue and/or fresh biopsy is required pre-treatment for all patients. Additional optional on-study biopsy taken at the time of disease progression. ALK alterations will be assessed centrally. Testing for other targets, such as MET, EGFR, KRAS, or others, may be performed on samples on an exploratory basis. Mutational analysis may also be performed. If additional slides or tissue are available, other exploratory analyses may also be performed. Note that patients who develop a skin rash thought to be related to study drug, are also encouraged to have a skin biopsy and digital photos obtained for evaluation. Refer to the Study Laboratory Manual for sample processing and shipping instructions.

q. Patients will be assessed according to RECIST v1.1 criteria (systemic and CNS lesions). Assessments by CT and MRI of the brain will be performed after every even cycle of treatment. All assessments should be performed within 7 days prior to Day 1 of that next odd cycle. However, at Cycle 19, the frequency will increase to every 12 weeks (+/- 1 week due to impact of COVID-19 pandemic) Tumor lesions followed on physical examination must be assessed on Day 1 of each cycle and at the End of Trial Treatment visit.

r. All patients will undergo the end of treatment assessments listed within 30 days after treatment ends due to completion of the planned trial treatment period, or once a patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the trial physician. If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no trial treatment is administered, that visit may fulfill the End of Trial Treatment visit. After withdrawal from or completion of protocol treatment, patients must be followed for adverse events (and concomitant medications) for 30 calendar days after the last dose of study drug. For patients who discontinue treatment without radiographic progression per RECIST 1.1 (e.g., in patients who discontinue treatment for clinical progression or adverse reactions), disease assessments should continue approximately every 8 weeks after study treatment until radiographic disease progression or alternate therapy is given.

s. Optional biomarker blood samples for exploratory evaluation of nucleic acid (such as DNA, RNA) and/or protein will be obtained. In addition to testing for ALK, other resistance mechanisms may be evaluated. Approximately 10 mL of blood will be obtained in each of 2 EDTA tubes (total of approximately 20 mL of blood). These samples should be drawn

pre-dose on Cycle 1 Day 1, Day 1 of each cycle from Cycle 2 through end of treatment, and at the end of trial treatment. Refer to the Study Laboratory Manual for sample processing and shipping instructions.

t. Day 1 of each cycle after the first should occur 28 days ± 3 days after Day 1 of the prior cycle.

u. QoL will assessed at Screening, Baseline (see footnote b), Cycle 2 Day 1, Cycle 3 Day 1, then approximately every 8 weeks, and at the End of Trial Treatment visit.

v. Patients with known hepatitis B must be HBeAg and HB viral DNA negative for enrollment. Note that, because of the high prevalence, all patients in the Asia-Pacific region (except Australia, New Zealand, and Japan) must be tested and, if HBsAg positive, must be HBeAg and HB viral DNA negative for enrollment.

w. In addition to the other pregnancy testing noted, for countries where it is required (e.g., **Belgium, , Poland and Germany**), beginning with Cycle 2, pregnancy testing must also be performed on the Day 1 assessment of every cycle, and in **Belgium/Germany** 30 days after the end of treatment, in women of childbearing potential.

x. Follow-up for survival should be obtained in all patients after completion of study treatment. This should be done approximately every 6 months. Note: patients that end treatment for reasons other than disease progression should continue to be followed every 8 weeks (see section 9.6.4.1). Once disease progression occurs per RECIST criteria, then follow for survival approximately every 6 months."

y. Patients beyond Cycle 19, should attend the next subsequent visit in the new 12 week schedule though the visit may actually be sooner than 12 weeks (i.e. if a patient is affected by the new 12-week schedule from cycle 21, the next visit is on cycle 22 based on a 12-week schedule starting by default from cycle 19). If the visit is sooner than 12 weeks, then the imaging at this visit is not necessary, however imaging should resume at the next 12 week interval and continue thereafter.

STATISTICAL ANALYSIS PLAN (SAP)

XALT3: PHASE 3 RANDOMIZED STUDY COMPARING ENSARTINIB TO CRIZOTINIB IN ANAPLASTIC LYMPHOMA KINASE (ALK) POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

X396-CLI-301

Version 3.0 (Final), 14-OCT-2019

Sponsor:

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[redacted]

Study Drug: X-396, **Sponsor Clinical Trial Protocol Number:** X396-CLI-301

SAP APPROVAL FORM

Document Title:	**Statistical Analysis Plan (SAP)**
Protocol Number:	**X396-CLI-301**
Study Title:	**XALT3: Phase 3 Randomized Study Comparing Ensartinib to Crizotinib in Anaplastic Lymphoma Kinase (ALK) Positive Non-Small Cell Lung Cancer (NSCLC) Patients**
Document Date:	**14-0CT-2019**
Document Version:	**3.0**

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Chief Medical Officer, Xcov ***CONFIDENTIAL***

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LIST OF ABBREVIATIONS

AE	adverse event
ALT (SGPT)	alanine aminotransferase
ALK	anaplastic lymphoma kinase
aPTT	activated partial thromboplastin time
AST (SGOT)	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BID	twice daily
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
CBC	complete blood cell count
CI	confidence interval
CNS	central nervous system
CR	complete response
CSR	Clinical study report
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DMC	data monitoring committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EPHA2	ephrin A2 kinase
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
HB	hepatitis B
HBeAg	hepatitis B e-antigen
HBsAg	hepatitis B surface antigen
ICF	informed consent form
ICH	International Conference on Harmonization
IHC	immunohistochemistry
INR	international normalized ratio
IRR	independent radiology review
ITT	intent-to-treat
IVRS	interactive voice response system
LCSS	Lung Cancer Symptom Scale
LD	longest diameter
mg	milligram
ms	millisecond
MedDRA	Medical Dictionary for Drug Regulatory Activities
mITT	modified intent-to-treat
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non-small-cell lung cancer
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PDy	pharmacodynamic
PE	physical examination

PFS	progression-free survival
PopPK	population pharmacokinetic
PR	partial response
PT	prothrombin time
QD	once daily
QTc	corrected QT interval
QTcF	Fridericia corrected QT interval
QoL	quality of life
RBC	red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TTR	time to response
TTR	time to deterioration
WBC	white blood cells

1. SCOPE

This Statistical Analysis Plan (SAP) is created based on Protocol X396-CLI-301 Version 4.0, 02 Oct 2019, and it describes in detail the statistical methodology and the statistical analyses to be conducted for the above-mentioned protocol. The following summarizes the protocol and amendment history:

Version	**Approval Date**	**Salient Changes, if any***
Original Protocol (Version 1.0)	September 28, 2015	N/A
Version 1.1	March 24, 2017	-Clarify follow-up of patients after End of Treatment (Section 9.4) -Add NE under CNS lesions in Best Overall Response table (Section 11.3.2) -Add stopping rules for futility at the interim analysis (Section 13.11)
Version 2.0	January 22, 2018	-Changed study entry requirement for ALK testing to central testing only (Synopsis, Section 5.1 and Section 9.9.1) -Adjusted numbers of patients for the ITT and mITT populations and resulting power and hazard ratio assumptions (Synopsis and Section 13.11) -Eliminated RANO-BM evaluations for CNS lesions; now to be evaluated just by CNS RECIST 1.1 (Sections 11, 13.5 and 13.7.2) -Upversion of MedDRA dictionary (Section 13.10) -Clarified reasons patients may be discontinued from trial.
Version 3.0	June 19, 2019	-Replace IA for futility at 50% (95/190) in mITT population with IA for efficacy at 67% (128/190) in ITT population using O'Brien-Fleming LanDeMets (DeMets and Lan, 1994) alpha spending function to control overall alpha at 0.05 2-sided -Add CNS ORR and time to CNS progression as key secondary endpoints and implement hierarchical gatekeeping testing procedure to control the multiplicities -Use the same event size assessment based on ITT instead of mITT

Version 4.0	October 2, 2019	-Changed order of secondary endpoints and specified that overall survival will be formally tested before the other secondary endpoints -Addition of efficacy biomarkers to exploratory endpoints -Adjusted the interim analysis trigger to be 75% of the planned PFS events by IRR -Removed hierarchical gatekeeping of CNS ORR, time to CNS progression, ORR and OS.
* Changes expected to require accommodation in analysis plan.		

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objectives of this trial are:

- To evaluate the efficacy and safety of ensartinib vs. crizotinib in patients with ALK-positive NSCLC that have received up to 1 prior chemotherapy regimen and no prior ALK TKI.

2.2. Secondary Objectives

The secondary objectives of this trial are:

- To obtain additional pharmacokinetic (PK) data on ensartinib from sparse PK sampling from patients at selected sites.

2.3. Exploratory Objectives

Exploratory objectives of this trial are:

- To compare the quality of life (QoL) in patients receiving ensartinib vs. crizotinib.
- To evaluate the status of exploratory biomarkers and correlate with clinical outcome.
- To obtain germline DNA samples for possible pharmacogenetic analysis in the event that outliers with respect to efficacy, tolerability/safety, or exposure are identified.

3. STUDY DESIGN

3.1. Overall Plan

This is a Phase 3, open-label, randomized study of the Anaplastic Lymphoma Kinase (ALK) inhibitors ensartinib and crizotinib given as single agents to adult patients with ALK-positive non-small-cell lung cancer (NSCLC). Patients will be randomized 1:1. Up to 316 patients in the intent-to-treat (ITT) population are expected to be enrolled in this study at up to 170 sites worldwide.

The study drugs will be given orally daily on a 28-day schedule. Ensartinib 225 mg will be given once daily (QD) or crizotinib 250 mg will be given twice daily (BID).

3.2. Study Population

Up to 316 patients are planned to be enrolled in the study. Patients must be ALK positive by local test prior to submitting tissue to the central lab. Randomization will occur after ALK positive confirmation is received from the central lab. Patients may have received up to 1 prior chemotherapy regimen for metastatic disease, which may also include maintenance therapy. Brain metastases are allowed if asymptomatic at study baseline. Patients who have previously received an ALK tyrosine kinase inhibitor (TKI) are excluded. Section 5 of the protocol contains a complete list of the inclusion and exclusion criteria.

3.3. Randomization, Stratification and Blinding

This study will employ a 1:1 randomization. Patients will be stratified based on the following factors:

- Prior chemotherapy: none vs. 1 prior regimen
- Performance Status: 0 or 1 vs. 2
- Central nervous system (CNS) metastases at baseline: no vs. yes
- Geographic region: Asia vs. rest of the world

Randomization will be conducted centrally via an interactive voice response system (IVRS) using a permuted block randomization. This procedure will ensure balance by treatment arm for the stratification factors of interest.

To ensure sufficient numbers of patients from the rest of the world, enrollment will be capped in the Asian region to no more than 60% of the planned number of patients.

The randomization schedule will be developed by an independent third-party vendor to ensure that the study patients, investigators, study site personnel, safety laboratory personnel, central imaging readers, and representatives of Xcovery involved in the conduct and/or management of the trial remain blinded to treatment assignment prior to randomization. Randomization details will be specified in a separate Randomization Schedule Specification document. Until the time of unblinding, the randomization schedule will be kept strictly confidential.

3.4. Study Assessments

Table 1 presents the visit schedule and procedures of the study to be conducted at each visit.

Table 1 (Appendix E from Protocol): Schedule of Assessments for Protocol X396-CLI-301

Procedures	Pre-Treatment	TRIAL TREATMENT						End of Trial Treatment[r]	30 Days Post End of Treatment and Survival
	Screening/ Baseline	Cycle 1 Cycle = approx. 28 days	Cycle 1	Cycle 2	Cycle 3 Through Cycle 18		Cycle 19 Through End of Treatment		
		Day 1 (pre-dose)	Day 15	Day 1[t]	Day 1 (Every 4 Weeks)[t]	Every 2 Cycles (Every 8 Weeks)[t]	Every 2 Cycles (Every 8 Weeks)[t]		
TESTS & OBSERVATIONS									
Informed Consent[a]	X[a]								
Medical history (including smoking history)	X								
Physical examination, including whole body skin exam, neuro exam for patients with CNS disease, vital signs, height, weight[c]	X	X[b]	X	X	X		X	X	
ECOG Performance Status	X	X[b]	X	X	X		X	X	
EORTC C30/LC13 QoL questionnaire & LCSS	X	X[b]		X		X[u]	X[u]	X	
Adverse event evaluation	X	X	X	X	X		X	X	X[r]
Concomitant medication review	X	X	X	X	X		X	X	X[r]
LABORATORY TESTS									
CBC, including differential and platelets[d]	X	X[b]	X[d]	X[d]	X		X	X	
Clinical chemistry[e]	X	X[b]	X[e]	X (and at Cycle 2 Day 15)[e]	X		X	X	
Coagulation tests[f]	X	X[b]		X		X	X	X	

Total testosterone		X		X	X[g]			X	
HBsAg, HBeAg, HB viral DNA[v]	X[v]								
12-lead ECG[h]	X	X		X		X	X	X	
Urinalysis[i]	X	X[b]		X				X	
Serum or urine pregnancy test[j]	X			X[w]	X[w]		X[w]	X	X[w]
PK blood[k]		X		X	X (Cycle 3 only)			X	
Biomarker blood sample collection[s]		X		X	X		X	X	
PG blood sample[l]	X[l]								
Tumor tissue sample[p]	X							X[p]	
DISEASE ASSESSMENT									
CT scan of the chest, abdomen, pelvis[m,q]	X					X	X	X	
MRI of the brain[n,q]	X					X	X	X	
Bone scan[o]	X								
Follow-up for survival									X[x]

Table 1 (Appendix E from Protocol): Schedule of Assessments for Protocol X396-CLI-301 (continued)

a. Informed Consent must be obtained ≤28 days prior to the initiation of trial treatment.

b. The screening physical examination, ECOG performance status, QoL questionnaires, hematology, blood chemistry, coagulation, and urinalysis tests should be done ≤28 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1, they do not have to be repeated. If these must be repeated for Cycle 1 Day 1, they can be completed ≤ 3 days prior to Cycle 1 Day 1.

c. Physical examinations will include measurements of weight and vital signs (resting heart rate, blood pressure, respiratory rate, temperature). Physical examinations will also include a whole body skin examination in all patients and a neurologic exam for patients with CNS metastases at baseline (document clinically significant findings as for any other clinically significant findings from physical exam) and will be done on Day 1 of each cycle. Note that patients who develop a skin rash thought to be related to study drug, are encouraged to have a skin biopsy and digital photos obtained for evaluation. Note, also, that vital signs should be assessed before blood collection. At the screening visit only, height will also be recorded.

d. Hematology parameters include the following laboratory tests: complete blood cell count with 3-part differential (i.e., total neutrophil count including bands, lymphocytes, monocytes), hemoglobin, hematocrit and platelets. Note: Where required (e.g., **Czech Republic and Germany**, this should be repeated weekly during Cycle 1 and on Cycle 2 Days 1 and 15).

e. Blood chemistry must include glucose, BUN, creatinine, sodium, potassium, magnesium, chloride, calcium, CO_2, alkaline phosphatase, AST (SGOT), ALT (SGPT), total bilirubin, total protein, albumin, phosphorus, uric acid. This should also be repeated on C2 Day 15, then every cycle and as clinically indicated (e.g. more frequent for level 2, 3 or 4 increases of ALT, AST or bilirubin). In addition, where required, this should be obtained more frequently during the first 2 cycles, (e.g., weekly in the **U.K**. **and Germany)**.

f. Coagulation tests include PT, PTT, INR.

g. Total testosterone will be collected from male patients prior to dosing at Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1 and at the end of trial treatment.

h. Three 12-lead ECGs will be collected approximately 5 minutes apart at the screening visit. On Cycle 1 Day 1, three ECGs will be collected approximately 5 minutes apart pre-dose. Thereafter, three sequential (approximately 5 minutes apart) pre-dose 12-lead ECGs will be collected on the Cycle 2 Day 1 and Cycle 3 Day 1 visits, and then approximately every 8 weeks, and at the end of trial treatment visit. In addition, for patients randomized to ensartinib, ECGs will be obtained on Cycle 1 Day 1 and Cycle 2 Day 1 approximately 4 hours (± 1 hour) after dosing regardless of food/fasting. Note that ECGs should be obtained before blood collection.

i. A urine dipstick (pH, specific gravity, blood, protein, glucose) will be done at screening/baseline, Cycle 2 Day 1, and the end of trial treatment visit.

j. A serum or urine pregnancy test will be performed within 1 week prior to initial treatment, if a menstrual cycle is missed during treatment or pregnancy is otherwise suspected, and at the end of treatment visit only for women of childbearing potential.

k. PK blood samples will be collected from ensartinib patients at participating sites. To characterize differences in Asian populations, PK sampling will be required at sites in China for ensartinib patients. Samples will be collected at pre-dose and approximately 4 hours (± 1 hour) after dosing on Cycle 1 Day 1 and Cycle 2 Day 1, whether ensartinib was taken with or without food, pre-dose on Cycle 3 Day 1, and at the end of trial treatment visit if the patient had taken the last dose of study drug the day before the end of trial treatment visit.

l. One pharmacogenetic blood sample (one EDTA tube) will be collected at baseline from as many ensartinib patients as possible for possible future testing. The baseline sample must necessarily have been completed after randomization to ensartinib. As a result, the sample may be pulled on Cycle 1 Day 1, however, it must be prior to dosing.

m. Patient will have CT scan at screening/baseline (≤28 days prior to initiation of treatment), approximately every 8 weeks, whenever disease progression is suspected, and at end/withdrawal from study. For patients who discontinue treatment without radiographic progression per RECIST 1.1 (e.g., in patients who discontinue treatment for clinical progression or adverse reactions), disease assessments should continue approximately every 8 weeks after study treatment until radiographic disease progression or alternate therapy is given. (Note: MRI may be used as an alternative to abdomen and pelvis CT scans; the modality used at screening/baseline should be identical at each disease assessment).

n. Gadolinium-enhanced, T1-weighted MRI of brain required for all patients (unless there is a contraindication for MRI, in which case CT with and without contrast may be used). Screening/baseline scans should be performed ≤28 days prior to initiation of treatment and approximately every 8 weeks, whenever disease progression is suspected, and at the end/withdrawal from study. For patients who discontinue treatment without radiographic progression (e.g., in patients who discontinue treatment for clinical progression or adverse reactions), disease assessments should continue approximately every 8 weeks after study treatment until radiographic disease progression or alternate therapy is given.

o. Bone scan should be obtained in all patients at screening/baseline (≤28 days prior to initiation of treatment) and repeated during the study if patients become symptomatic or if needed to confirm CR. Note: PET scan may be used as an alternative to bone scan, but must be performed at screening and subsequent scans for consistency.

p. Adequate archival tissue and/or fresh biopsy is required pre-treatment for all patients. Additional optional on-study biopsy taken at the time of disease progression. ALK alterations will be assessed centrally. Testing for other targets, such as MET, EGFR, KRAS, or others, may be performed on samples on an exploratory basis. Mutational analysis may also be performed. If additional slides or tissue are available, other exploratory analyses may also be performed. Note that patients who develop a skin rash thought to be related to study drug, are also encouraged to have a skin biopsy and digital photos obtained for evaluation. Refer to the Study Laboratory Manual for sample processing and shipping instructions.

q. Patients will be assessed according to RECIST v1.1 criteria (systemic and CNS lesions). Assessments by CT and MRI of the brain will be performed after every even cycle of treatment. All assessments should be performed within 7 days prior to Day 1 of that next odd cycle. Tumor lesions followed on physical examination must be assessed on Day 1 of each cycle and at the End of Trial Treatment visit.

r. All patients will undergo the end of treatment assessments listed within 30 days after treatment ends due to completion of the planned trial treatment period, or once a patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the trial physician. If treatment is discontinued because of toxicity or any other reason(s) at a treatment visit and no trial treatment is administered, that visit may fulfill the End of Trial Treatment visit. After withdrawal from or completion of protocol treatment, patients must be followed for adverse events (and concomitant medications) for 30 calendar days after the last dose of study drug. For patients who discontinue treatment without radiographic progression per RECIST 1.1 (e.g., in patients who discontinue treatment for clinical progression or adverse reactions), disease assessments should continue approximately every 8 weeks after study treatment until radiographic disease progression or alternate therapy is given.

s. Optional biomarker blood samples for exploratory evaluation of nucleic acid (such as DNA, RNA) and/or protein will be obtained. In addition to testing for ALK, other resistance mechanisms may be evaluated. Approximately 10 mL of blood will be obtained in each of 2 EDTA tubes (total of approximately 20 mL of blood). These samples should be drawn pre-dose on Cycle 1 Day 1, Day 1 of each cycle from Cycle 2 through end of treatment, and at the end of trial treatment. Refer to the Study Laboratory Manual for sample processing and shipping instructions.

t. Day 1 of each cycle after the first should occur 28 days ± 3 days after Day 1 of the prior cycle.

u. QoL will assessed at Screening, Baseline (see footnote b), Cycle 2 Day 1, Cycle 3 Day 1, then approximately every 8 weeks, and at the End of Trial Treatment visit.

v. Patients with known hepatitis B must be HBeAg and HB viral DNA negative for enrollment. Note that, because of the high prevalence, all patients in the Asia-Pacific region (except Australia, New Zealand, and Japan) must be tested and, if HBsAg positive, must be HBeAg and HB viral DNA negative for enrollment.

w. In addition to the other pregnancy testing noted, for countries where it is required (e.g., **Belgium, Poland and Germany**), beginning with Cycle 2, pregnancy testing must also be performed on the Day 1 assessment of every cycle, and in **Belgium/Germany** 30 days after the end of treatment, in women of childbearing potential.

x. Follow-up for survival should be obtained in all patients after completion of study treatment. This should be done approximately every 3 months for the first year after the end of treatment and then approximately every 6 months. Note: patients that end treatment for reasons other than disease progression should continue to be followed every 8 weeks. Once disease progression occurs per RECIST criteria, then follow for survival approximately every 3 months for the first year and then approximately every 6 months."

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4. SAMPLE SIZE DETERMINATION

This study will enroll up to 316 ITT patients, using a 1:1 randomization. A sample size of 266 will allow detection of a hazard ratio of 0.625, with 90% power and a 2-sided alpha of 0.05 in the ITT population. This estimate assumes a median PFS of 10 months in the crizotinib arm (based on the assumption that approximately 2/3 of patients will be chemotherapy-naïve), with an improvement to 16 months in the ensartinib arm, and 27month accrual period with 12 months of additional follow-up. The final analysis will be performed after 190 PFS events have been observed in the ITT population. An interim analysis will be performed after approximately 75% of the planned PFS events have occurred (143 of 190 total events).

5. STUDY ENDPOINTS

5.1. Efficacy Endpoints

5.1.1. Primary Efficacy Endpoints

The primary efficacy endpoint is progression-free survival (PFS) as assessed by independent radiology review (IRR) based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria (Eisenhauer 2009). All disease assessments will be evaluated by central readers blinded to treatment assignment and other clinical study data during the study, according to procedures outlined in a separate Imaging Review Charter (2017).

Two separate outcomes will be determined from radiologic imaging. The outcomes will include a standard RECIST 1.1 evaluation of all sites of disease (systemic as well as CNS), called RECIST 1.1 Combined Outcome for this protocol. PFS derived from RECIST 1.1 Combined Outcome is the primary endpoint of the study. CNS metastases will also be assessed separately using RECIST v. 1.1 criteria, called RECIST 1.1 CNS, and will encompass only brain lesions, as a secondary efficacy endpoint.

The approach to both RECIST-based disease response assessments will be the standard application of the RECIST 1.1 criteria, with the difference in the 2 outcomes centered on the anatomic sites of disease from which target, non-target and new lesions are identified. The standard approach and definitions of response and progression will remain the same for both outcomes. Refer to section 11 of the protocol for definitions and guidelines in assessing disease response and progression using RECIST 1.1. Refer to Section 5.1.2.2 of the SAP for determination of Best Overall Response.

PFS, derived from either RECIST 1.1 Combined Outcome, is defined as the time in months from date of randomization to the first date of progression or death due to any cause. The date of progression is the date of a new lesion or the date of radiological measurements of target lesions that meets criteria for progression. Suspected clinical progression should be confirmed by radiologic assessment. Patients who are alive and have not progressed or are lost to follow-up as of a data analysis cutoff date will be right censored.

Hence, PFS in days = (date of progression, death or censor date) – (date of randomization) + 1. PFS in months = (PFS in days)/30.4275.

Censoring rules will include the following:

- Patients last known to be alive and progression-free will be censored at the date of the last adequate objective disease assessment.
- Patients with no on study disease assessments will be censored at the date of randomization unless death occurred prior to the first planned assessment (in which case the death is an event). Specifically, deaths on or before Day 63 are events (2 cycles of 28 days each plus 6-day window); deaths after Day 63 would not be considered events and will be censored at the date of randomization.

- Patients with inadequate baseline disease assessment will be censored at the date of randomization.
- Patients who received alternate therapy prior to progression will be censored at the date of the last adequate objective assessment prior to receiving alternate therapy.
- Patients who missed two or more consecutive objective disease assessments since the last adequate response assessment and who have a PFS event (death or progression) after the missing assessments and prior to a subsequent adequate objective assessment of non-progression are censored at the time of last adequate objective assessment prior to the missing assessments.
- Patients who stop treatment for undocumented progression, toxicity or reasons other than documented PD will be censored at last adequate disease assessment.

5.1.2. Key Secondary Efficacy Endpoints

5.1.2.1. Overall Survival

Overall survival (OS) is defined as the time in months from date of randomization to death due to any cause. Patients who are alive or lost to follow-up as of a data analysis cutoff date will be right-censored. The censoring date will be determined from the patients' date of last contact (i.e., last known alive date) or data analysis cutoff date, whichever event occurs first.

5.1.2.2. CNS Response by Independent Radiology Review

For patients with CNS metastases at baseline, CNS response by IRR is defined using RECIST 1.1 criteria (RECIST 1.1 CNS). A best overall CNS response will be determined using the same criteria as best overall response but applied only to CNS metastases.

5.1.2.3. Time to CNS Progression by Independent Radiology Review

Time to CNS progression is defined as the time in months from date of randomization to the first date of documented CNS progression by RECIST 1.1 criteria. This includes patients with CNS metastases at baseline as well as those without CNS metastases at baseline but subsequently develop CNS metastases. The same censoring rules for PFS will apply to time to CNS progression except that only CNS disease will be considered.

5.1.2.4. Objective Response by Independent Radiology Review

Objective response rate (ORR) is defined as the proportion of patients in ITT population who have an objective response using RECIST 1.1 criteria by IRR. An objective response is defined as a best overall response of CR or PR. In order, the categories for best overall response are:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)

- Progressive Disease (PD)
- Not Evaluable (NE)

The numerator for the proportion will be the number of patients within a treatment group with a best response of CR or PR, and the denominator will be number of ITT patients. Patients who do not have an adequate response assessment for any reason will be counted as a non-responder. As supportive analysis, ORR will also be calculated among subjects who have measurable lesions at baseline.

The procedures regarding the independent review and adjudication of response assessments will be outlined in a separate Imaging Review Charter (2017). CNS metastases will be assessed using RECIST 1.1 criteria. Refer to Section 11 of the protocol for RECIST 1.1 criteria for measurable disease, measuring lesions, and determining disease response and progression at each assessment period.

Evaluation of Best Overall Response

Evaluation of best overall response considers both systemic disease and CNS metastases (RECIST 1.1 Combined Outcome). The best overall response is the best response recorded from the date of randomization until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria, per protocol Section 9.6.4.1.

For a best response of CR or PR or SD, the response must be documented to have lasted for a minimum of 4 weeks, i.e., on 2 assessments performed at least 4 weeks apart. In the case of an assessment of CR at one visit, followed by a PR at a visit that is at least 4 weeks apart, the best response is PR. Similarly, a PR followed by a CR with no subsequent confirmation has a best response of PR. An assessment of SD at one visit, followed by a PD at a visit that is at least 4 weeks apart, the best response is PD. The following table, taken from Section 11.3 of the protocol, defines how overall response for systemic disease and CNS disease at an on-study visit is determined using RECIST 1.1.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-CR/Non-PD or NE	No	PR
SD	Non-CR/Non-PD or NE	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Any	Any	Yes	PD

5.1.3. Other Secondary Efficacy Endpoints

5.1.3.1. Time to Response by Independent Radiology Review

Time to response (TTR) is defined for patients who achieve a confirmed objective response of CR or PR as the time in months from date of randomization to the date of the first recorded, confirmed objective response (CR or PR) as determined by IRR.

5.1.3.2. Duration of Response by Independent Radiology Review

Duration of objective response is defined for patients who achieve a confirmed objective response of CR or PR from the date of the first recorded, confirmed objective response (CR or PR) by IRR to the first date of documented disease progression. The same censoring rules for PFS will apply to duration of objective response.

5.1.3.3. Duration of Disease Control by Independent Radiology Review

For patients with a best overall response of SD or better by IRR, duration of disease control is defined from the date of the first recorded response of CR, PR or SD to the first date of documented disease progression. The same censoring rules for PFS will apply to duration of disease control.

5.1.3.4. Investigator-assessed Efficacy Endpoints

Investigator-assessed secondary efficacy endpoints are:

- PFS based on investigator assessment
- ORR based on investigator assessment
- Time to response based on investigator assessment
- Duration of response and disease control based on investigator assessment
- CNS Response Rate based on investigator assessment
- Time to central nervous system (CNS) progression based on investigator assessment

The definitions of these endpoints, including censoring rules, are the same as the corresponding centrally reviewed endpoints, except the assessment is performed by the investigator. The same censoring rules for PFS and duration of response or disease control will apply, except as noted below for a competing risks analysis of time to CNS progression.

5.1.4. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints are:

- Patient reported time to deterioration (TTD) as measured by the European Organization for Research and Treatment of Cancer (EORTC) C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale (LCSS)
- Patient reported health-related quality of life (HRQoL) as measured by changes from baseline in the EORTC C30/LC13 QoL questionnaire and Lung Cancer Symptom Scale at each visit

The EORTC quality of life questionnaire (QLQ) is an integrated system for assessing the health-related quality of life (QoL) of cancer patients participating in international clinical trials. The core questionnaire within the QLQ is the C30. Scoring of version 3.0 of the 30-item C30 questionnaire will be done according to the EORTC QLQ-C30 Scoring Manual, and will present include a Global Health Status score, Functional Scale scores (Physical Functioning, Role Functioning, Emotional Functioning, Cognitive Functioning, Social Functioning) and Symptom Scale scores (Fatigue, Nausea and Vomiting, Pain, Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea, Financial Difficulties) (Fayers, 2001).

The Lung Cancer Module, EORTC QLQ-LC13, is a supplementary 13-item questionnaire module that is employed in conjunction with the QLQ-C30 for use in lung cancer clinical trials, in which the patient assesses symptoms or problems experienced over the past week. The QLQ-LC13 incorporates one multi-item scale to assess dyspnea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. Scoring of QLQ-LC13 questionnaire will be done according to the EORTC QLQ-LC13 Scoring Manual (Bergman, 1994))

The individual items on both EORTC questionnaires will be scaled and scored according to the EORTC QLQ-C30 Scoring Manual (Fayers, 2001). The raw scores will be transformed to a linear scale ranging from 0 to 100, where higher scale scores indicate better HRQoL for the global health status and functioning scales, and worse HRQoL for the symptom scales. Differences from baseline of at least 10 points will be classified as the minimum clinically meaningful change in an HRQoL measure (Osoba, 1998; Taphoorn, 2005; Maringwa, 2011). Changes of more than 20 points will be classified as large effects. For example, an increase of 10 points on a functional scale will represent a moderate improvement, whereas a decrease of 10 points will represent moderate worsening. Changes of less than 10 points will be regarded as no change, or as clinically irrelevant.

The functional scales will be scored as follows:

$$Score = \left(1 - \frac{RS - 1}{range}\right) \times 100$$

where *range* is the difference between the possible maximum and minimum response to individual items. NB: Most items take values from 1 to 4, giving *range* = 3. Raw score (RS) is the mean of the component items:

$$RS = + + + +(I_1 I_2 \quad I_3 \ldots I_n)/n$$

Similarly, the symptom scales/items and global health status will be scored as follows:

$$Score = \{(RS - 1)/range\} \times 100$$

For multi-item scales, if at least half the items in the scale are complete, then the scale score will be calculated based on the items for which data are available. Otherwise, the scale score will be set to missing. Under this approach, none of the single-item measures will be imputed.

Table 1. Scoring the QLQ-C30 (version 3.0)

Scales/Items	Number of Items	Item Range	Item Numbers
Global health status Global health status	2	6	29, 30
Functional scales			
Physical functioning	5	3	1 to 5
Role functioning	2	3	6, 7
Emotional functioning	4	3	21 to 24
Cognitive functioning	2	3	20, 25
Social functioning	2	3	26, 27
Symptom scales/items			
Fatigue	3	3	10, 12, 18
Nausea and vomiting	2	3	14, 15
Pain	2	3	9, 19
Dyspnea	1	3	8
Insomnia	1	3	11
Appetite loss	1	3	13
Constipation	1	3	16
Diarrhea	1	3	17
Financial difficulties	1	3	18

Table 2. Scoring the QLQ-LC13

Scales/Items	Number of Items	Item Range*	Item Numbers
Symptom scales / items			
Coughing 1 3 31 Hemoptysis 1 3 32			
Dyspnea [a] 3a 3 33 - 35 Sore mouth 1 3 36 Dysphagia 1 3 37			
Peripheral neuropathy	1	3	38
Alopecia	1	3	39
Pain in chest	1	3	40
Pain in arm or shoulder 1 3 41 Pain in other parts 1 3 42 Pain medication intake 1 3 43			

* "Item range" is the difference between the possible maximum and the minimum response to individual items. All items are scored 1 to 4, giving range = 3. [a] The dyspnea scale should only be calculated if all three items have been answered.

Baseline HRQOL assessments will be administered to patients prior to initiation of study treatment. HRQOL assessments are planned for day 1 of Cycle 2 and then Day 1 of alternating 28 cycles, thereafter. HRQOL assessments also are planned at the treatment visit.

Summarization of the HRQOL data will be based on month of follow-up (defined in integers) rather than using the nominal visit indicated on the CRF. During the adjuvant and maintenance treatment phases, 28-day treatment cycles are planned. As such, month of follow-up will be determined using 28-day months. For HRQOL assessments performed after the first dose of study treatment, the follow-up month will be derived as follows based on the SAS function, round(.):

Month = round((HRQOL assessment date – first dose date + 1) ÷ 28, 1)

If multiple HRQOL assessments are associated with the same month, the assessment performed closest to the planned study day will be used for purposes of summarizing the data. If two measurements are equidistant from the planned study day, the measurement occurring prior to the planned study day will be used for summarization.

The Lung Cancer Symptom Scale is a QoL assessment designed for use in clinical trials in patients with lung cancer. Patients are asked to assess 6 symptoms (loss of appetite, fatigue, coughing, shortness of breath, blood in sputum, pain) and their effect on symptomatic distress, functional activities, and global quality of life on 9 individual visual analog scales (normalized to a 100-point scale). An average of the aggregate score of all 9 items is reported as a total score. In addition, a sub-score using the mean of all 6 major symptoms ("average symptom burden index") is reported, as well as each individual QoL item (ref http://www.lcss-ql.com).

Time to deterioration (TTD) is defined at the time from date of randomization to a worsening of at least 10 points (on a normalized 100-point scale) in each item score of the EORTC C30/LC13 and 15 mm in each item score of the LCSS (Osoba 1998). If a patient does not experience deterioration, TTD will be censored at the last non-missing

evaluation. Time to deterioration in patient-reported lung cancer symptoms of each of the individual symptoms: cough (single item QLQ-LC13) , chest pain (single item), dyspnea (single item (QLQ-C30) and multi-item subscales (QLQ-LC13)), pain in arm/shoulder (single item subscales QLQ-LC13) and fatigue (multi-item subscales QLQC30) , as measured by the EORTC QLQ-C30 and the supplemental lung cancer module (QLQLC13), as well as for the composite of the three following symptoms: cough, dyspnea (multi-item subscales QLQ-LC13) and chest pain will be analyzed as a time-toevent endpoint as described for PFS.

5.2. Safety Endpoints

The long-term safety of ensartinib in treated patients is assessed from physical examination (PE) findings, vital sign data, 12-lead electrocardiograms (ECGs), adverse events (AEs), serum chemistry, hematology, coagulation tests, urinalysis, and hormone testing (as applicable).

5.2.1. Adverse Events

All AEs of any patient during the trial will be reported in the electronic case report form (eCRF), and the Investigator will give his or her opinion as to the relationship of the AE to trial drug treatment (i.e., whether the event is related or unrelated to trial drug administration). AEs are to be recorded for each patient from their first dose of trial drug treatment. An event occurring after the patient has provided informed consent but before the first dose of study medication will be collected as part of the medical history. If a patient experiences a Serious Adverse Event (SAE) after signing informed consent, but prior to receiving study drug, the event does not need to be recorded as an SAE unless the investigator feels the event may have been caused by a protocol procedure. Other untoward events occurring in the framework of a clinical trial are also to be recorded as AEs.

All AEs regardless of seriousness or relationship to trial treatment, spanning from the start of trial treatment until 30 calendar days after discontinuation or completion of protocol-specific treatment as defined by the protocol for that patient, are to be recorded on the eCRF. However, once another anticancer therapy has been started, non-serious AEs during this time that are not thought by the investigator to be related to study treatment do not have to be reported.

Any Grade 3 or 4 laboratory abnormalities or any clinically significant Grade 1 or 2 laboratory value(s) should be recorded as an AE. If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded.

For both serious and non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study treatment administration. Intensity (ie, severity) for each AE, including any lab abnormality, will be graded by using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03:

- Grade 1 — Mild.
- Grade 2 — Moderate.
- Grade 3 — Severe.
- Grade 4 — Life-threatening consequences; urgent intervention indicated.
- Grade 5 — Death related to the AE.

Relatedness to study treatment administration will be determined by the Investigator, and will be graded as Related or Not Related.

Treatment-emergent adverse events (TEAEs) are defined as those AEs that occur, having been absent before first dose of study treatment, or have worsened in severity after the initiation of study treatment, up to either 30 days after the last dose.

Terminology from version 17.1 of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to assign System Organ Class (SOC) and Preferred Term classification to AEs and diseases, based on the original terms entered on the eCRF.

5.2.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed centrally at the indicated study visits in the Schedule of Events. Abnormal clinical laboratory results will be graded according to NCI CTCAE version 4.03, if applicable.

Clinical laboratory evaluations will be performed as outlined below:

Blood samples for analysis of the following clinical chemistry, hematologic, coagulation, and hormone parameters will be obtained:

- **Clinical Chemistry**

Sodium	Total protein
Potassium	Blood urea nitrogen (BUN)
Chloride	Creatinine
CO_2	Albumin
Calcium	Uric acid
Phosphorus	Magnesium
Glucose*	

* Fasting is recommended but not required.

- **Liver Function Tests**

Alkaline phosphatase	Total bilirubin
Aspartate aminotransferase (AST)	
Alanine aminotransferase (ALT)	

- **Hematology**

White blood cell count with differential	Hemoglobin
Platelet count	Hematocrit

- **Hepatitis Panel**
  HBsAg, HBeAg, and HB viral DNA
- **Coagulation**
  Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR).
- **Hormone Tests**

Females	**Males**
None	Total Testosterone

- **Urinalysis (dipstick and microscopic analysis)**
  Urine samples will be obtained for analysis of the following parameters:

pH	Specific gravity
Protein	Blood
Glucose	

5.2.3. Vital Signs and Patient Weight

Vital signs, including systolic/diastolic blood pressure, resting heart rate, respiratory rate and oral temperature will be measured in accordance with institutional standards. Vital signs and weight will be measured at the indicated study visits in the Schedule of Events.

Height will be measured at the Screening visit only.

5.2.4. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) in triplicate will be performed pre-dose at the indicated study visits in the Schedule of Events. The results will include heart rate (HR), RR interval, PR interval, QRS interval, QT interval, and Fridericia corrected QT interval (QTcF) interval. Any clinically important finding will be recorded on the appropriate eCRF. The investigator is responsible for providing the interpretation of all ECGs.

5.2.5. Other Safety Endpoints

A physical examination will be conducted at the indicated study visits in the Schedule of Events, and will include a whole skin body exam and neurologic exam for patients with CNS metastases. Patients who develop skin rash, particularly Grade 3 rash, will be

encouraged to have a skin biopsy and digital photos obtained for evaluation. The records of abnormal findings prior to and after the first of dose of study drug from physical examination will be captured in the medical history eCRF and adverse events eCRF, respectively. ECOG performance status will be collected at scheduled visits. Concomitant medications will be coded using the World Health Organization (WHO) drug dictionary.

For female patients of child-bearing potential only, a serum pregnancy test will be performed at the study visits indicated in the Schedule of Events.

5.3. Pharmacokinetic Endpoints

Sparse PK sampling for ensartinib patients will be performed in this trial at selected sites. Blood samples will be obtained at trough levels and at the approximate time of Cmax

(see Section 9.7 and Appendix E of the protocol). Plasma–concentration data from these samples will be analyzed using a PopPK approach using nonlinear mixed effects modeling. In addition, if appropriate, the sparse PK data may be evaluated with respect to efficacy outcomes and AEs considered to be drug-related to determine if a relationship between these might exist. Gender and age differences in toxicity may also be evaluated. PK data may be examined on an ongoing basis while the study is being conducted. Analysis of PK data will be conducted under a separate SAP and/or in an exploratory fashion.

5.4. Pharmacodynamic (PDy) and Biomarker Endpoints

Archived or fresh tumor tissue and blood samples will be collected and may be analyzed for exploratory biomarkers to assess correlation with clinical outcomes from study participants. In addition to tissue available at baseline (archival tissue or fresh biopsy), patients will be requested to undergo a post-treatment tumor biopsy upon progression. However, the post-treatment biopsy is optional. In addition, if possible, blood samples will be obtained from as many ensartinib patients as possible for pharmacogenetic analysis if outliers with respect to efficacy, tolerability/safety, or exposure are identified.

No formal statistical analysis of pharmacodynamics endpoints will be performed. Pharmacodynamic data from each assay will be listed and possible relationships between PK and pharmacodynamic variables may be explored. Biomarker data will be summarized using descriptive statistics. The results may be pooled with data from other studies to generate hypotheses to be tested in future studies.

6. ANALYSIS POPULATIONS

6.1. Analysis Population Definitions

The definitions of analysis populations are as follows:

- Intent to Treat (ITT) Population) - This population will comprise all patients who were randomized in the study whether or not the study drug was administered. Patients will be assigned to treatment groups based on the randomized drug assignment. This population will be the primary population analyzed for efficacy.
- Safety - This population will comprise all randomized patients who receive at least one dose of study drug. Patients will be assigned to treatment groups based on the actual drug received. If a patient receives drug from both arms, patient will be assigned to the ensartinib arm. This population will be analyzed for safety.
- Modified Intent-to-Treat (mITT) – The mITT Population will comprise all patients in the ITT population with confirmed ALK-positive disease by centrallyperformed FDA-approved assay. Patients will be assigned to treatment groups based on the randomized drug assignment. This population will be analyzed for PFS and overall survival.
- Per Protocol (PP) – The Per Protocol Population will comprise those ITT patients who meet major eligibility criteria affecting efficacy. This population will be analyzed for PFS and overall survival.

6.2. Protocol Deviations

Protocol deviations will be captured and reviewed by a medical monitor. Major protocol deviations will be categorized according to deviation reason and their impact on the Perprotocol population prior to the interim analysis in a separate document.

6.3. Treatment Misallocations

If patients were:

- Randomized but not treated, then they are by definition in the efficacy (ITT) analysis but excluded from the safety analysis.
- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomized treatment is missing, but they will be reported under the treatment they actually received for all safety analyses.
- Randomized but took incorrect treatment, then they will be reported under their randomized treatment group for all efficacy analyses, but will be reported under the treatment they received for all safety analyses. If a patient receives drug from both arms, patient will be reported under the Ensartinib arm.

7. GENERAL STATISTICAL CONSIDERATIONS

7.1. Data Summaries and Conventions

Data will be summarized by assigned or actual treatment group (ensartinib or crizotinib), as appropriate to the Analysis Population. Patient treatment groups will be identified as "Ensartinib" or "Crizotinib". Order of displaying treatments is: Ensartinib, Crizotinib.

Continuous endpoints will be summarized using descriptive statistics, which will include the number of patients with a valid measurement (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. Time-to-event endpoints will be analyzed using KaplanMeier product limit methods to estimate the survival distribution, median time-to-event with 95% confidence interval (Brookmeyer and Cowley 1982), patients at risk, patients with an event, the type of event (progressive disease or death), patients censored and survival probabilities at selected time points. Survival distribution plots using KaplanMeier methodology will be generated.

The safety endpoints will be listed and/or summarized by relevant time points, as appropriate.

In general, the baseline value for efficacy and safety variables is the last non-missing value before the first dose of study treatment. Data listings will be created to support each table and to present all data. Day 1 is the date of patient's first dose. The day immediately before Day 1 is Day -1. One month is considered 30.4275 days.

Unless otherwise specified, all statistical tests will be 2-sided and will be carried out at the alpha = 0.05 level of significance. For reporting purpose in all the statistical tables and in the clinical study report (CSR), p-values will be reported to four decimal places; pvalues less than 0.0001 will be reported as $p<0.0001$. Statistical significance of a statistical test is determined by comparing the p-value before rounding with the significance level.

The mean and median will be displayed to 1 decimal place greater than the original value and the measure of variability (eg, standard deviation) will be displayed to 2 decimal places greater than the original value.

All statistical analyses will be performed using SAS statistical software (SAS Version 9.4 or higher).

7.2. Adjustment for Covariates

Supportive analyses for PFS and OS included stratified log-rank tests using the stratification factors from randomization. To estimate a hazard ratio between treatment groups for time-to-event endpoints, Cox proportional hazard models will be employed using stratification factors as covariates in the model.

7.3. Handling of Dropouts or Missing Data

In general, missing data will not be imputed for any analysis, unless otherwise specified.

Besides the specified censoring rules (see Section 8.2.1), no further imputation for missing data will be applied to the efficacy endpoints.

Missing Dates

To calculate time since disease diagnosis, the date of diagnosis must have at least a nonmissing year. A partially missing date of diagnosis will be assigned the middle of the year (July 1), if day and month are missing and the 15th of the month if only the day is missing. If the year of diagnosis is the same as the randomization year, then January 1 will be assigned if the month is missing, and the 1st of the month will be assigned if only the day of month is missing.

For adverse events (AEs) with partially missing start dates, it may be necessary to impute an AE start date. For the partial date of AE start date (missing day and/or month and/or year), the following imputation rules will be applied:

- If year of the AE start date is missing, no date imputation will be made and the AE will not be considered treatment-emergent unless the investigator has deemed it to be treatment-related.
- If both day and month of the AE start date are missing, the day and month will be imputed with the day and month of the first study dose date if the year is equal to the year of first dose. Otherwise, the month and day is imputed as the first day of the year (01 Jan).
- If only day is missing, and if the year and month are equal to the first dose date, the day will be imputed as day of the first dose date. Otherwise, the day will be imputed as "01."

The same rule for AEs with partially missing dates will be applied to concomitant medications with partially missing dates.

7.4. Interim Analyses and Data Monitoring

One interim analysis is planned after approximately 75% of the total expected PFS events have been observed. An O'Brien-Fleming Lan-DeMets (DeMets and Lan, 1994) alpha spending function will be used to control at 0.05 2-sided. The interim will be performed after first 143 events have been observed and the primary endpoint of PFS will be tested at a 2-sided alpha level of 0.019.

The trial will utilize the services of a Data Monitoring Committee (DMC) to monitor patient safety and review the results of the interim analysis. A separate DMC Charter will define the DMC membership, its roles and responsibilities, and the process for providing feedback to the Sponsor.

7.5. Multicenter Studies

As few patients will be recruited per center, it would be impractical to include center effects in the statistical models. Region, instead of center, is included as a stratification factor at randomization and as an effect in analysis models, as appropriate. No multiplicity will be adjusted unless specified otherwise. Among key secondary endpoints,

only OS will be tested formally at 0.05 if the primary endpoints of PFS is statistically significant. Other secondary endpoints will be tested at 0.05 each and will be considered as exploratory.

7.6. Examination of Subgroups

The primary endpoint of PFS per IRR will be also analyzed in subgroups based on stratification variables, as well as demographic and baseline patient characteristics (e.g., age (<65 and ≥65), race, gender), and possibly exploratory biomarkers.

In each defined subgroup, the analysis will be carried out using the same type of methodology as described for the overall analysis of the corresponding endpoint. These results will be considered exploratory because of the multiplicity issue and also smaller sample sizes that cannot be pre-specified. P-values will not be determined; only summary statistics and the Confidence Interval (CI) will be presented. For subgroups without an adequate number of patients (typically subgroups with less than 20 patients), the analysis will not be performed.

8. STATISTICAL ANALYSIS

8.1. Study Population Data

8.1.1. Patient Disposition

Patient disposition will be summarized for each treatment group and in total for the ITT population. The total number of patients for each defined analysis population will also be tabulated.

Enrollment by region, country and center within country will be summarized. Treatment discontinuation and study follow-up completion/discontinuation will be summarized according to reasons documented in the CRF.

The reasons a patient may discontinue study treatment permanently include but are not limited to:

- Disease progression
- Condition requiring therapeutic intervention not permitted by the protocol
- Adverse event
- Lost to follow-up
- Patient withdraws consent
- Death
- Patient requests to discontinue treatment for reason other than Adverse Event
- Eligibility violation
- Investigator discretion
- Study terminated by sponsor
- Pregnancy
- Other
- Inability or unwillingness of the patient to comply with trial requirements

The reasons a patient may discontinue or be withdrawn from the study permanently include but are not limited to:

- Disease progression
- Condition requiring therapeutic intervention not permitted by the protocol
- Adverse event
- Lost to follow-up
- Patient withdraws consent
- Death
-
- Eligibility violation
- Investigator discretion
- Study terminated by sponsor
- Pregnancy
- Received other anti-cancer treatment
- Other
- Inability or unwillingness of the patient to comply with trial requirements

All the patient disposition data including end of treatment, end of study, and death report will be presented in the patient data listings.

8.1.2. Protocol Deviations

All important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment will be listed. Protocol deviations will be captured and reviewed by appropriate study personnel. Protocol deviations will be listed by treatment group, center and patient number, and categorized according to the deviation reason.

If a significant number of deviations occur, a summary table will be produced showing the number of patients for each deviation reason. Patients enrolled in the study with inclusion/exclusion violations will be reported with other protocol deviations.

All identified major protocol deviations will be reviewed prior to the snapshot (or DBL) by the statistician and the sponsor. Xcovery will approve the list of major protocol deviations which impact the efficacy. Patients with at least one major protocol deviation that have an impact on efficacy will be excluded from the per protocol population. These can fall into the categories as below:

- No baseline or post baseline tumor assessment
- Omission of tumor assessment
- Any disease/condition/treatment that interferes with study
- Patients with non-confirmed diagnosis of advanced or recurrent (or metastatic non-squamous NSCLC
- Life expectancy < 12 weeks
- ALK-positive, not determined by FDA-approved assay centrally
- Patient with non-measurable disease per RECIST at baseline
- Patient who did not receive any dose of study medication
- Patient who received incorrect study treatment or dose
- Patient who received/took prohibited concomitant medication
- Continuation of study drug when study drug should be discontinued per Protocol

8.1.3. Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized descriptively for the ITT and Safety populations. No formal statistical comparisons will be performed. Summaries for the Per-protocol population may also be presented if they are appreciably different from ITT.

Baseline demographics summary will include the following:

- Age in years, both as continuous and categories of 18 to 40, 41 to 65, and over 65. Age will be calculated as the number of years elapsed between birth date and the date of first informed consent, adjusted for whether the birthday has passed as of the day of informed consent. If the birth date is recorded only as a year, July 1 will be imputed for month and day of birth to calculate age.
- Gender (male or female)
- Race
- Ethnicity (Hispanic or Latino, or not Hispanic or Latino)

- Weight in kg
- Geographic region (Asia vs. rest of the world, by U.S., by EU and by country)
- Tobacco use (Never, Current, Former)
- ECOG performance status

Patient disease status will be summarized among the following items:

- Time since diagnosis (calculated relative to the date of informed consent, in months)
- Disease stage
- ALK status at baseline (local and central results)
- Measurable disease status at baseline
- Baseline RECIST 1.1 measurements
- Number of subjects with brain metastases at baseline
- Baseline EORTC C30/LC13 scores
- Baseline LCSS scores

Prior treatment summary will include the following:

- Prior surgical therapies
- Prior systemic therapies, including maintenance therapy
- Type of prior systemic therapies
- Prior radiation treatments

All demographic and baseline characteristic data including disease status, physical exam, medical and surgical history including smoking history, and disease history and prior treatment data will be presented in the patient data listings.

8.2. Efficacy Analyses

8.2.1. Analysis of Primary Efficacy Variables

The primary analysis of PFS by IRR will be conducted in the ITT Population. The null and alternative hypotheses for the primary endpoint are:

H_0: The distribution of PFS by IRR based on centrally read RECIST 1.1 criteria is equal between the ensartinib and crizotinib groups.

H_A: The distribution of PFS based on centrally read RECIST 1.1 criteria is not equal between the ensartinib and crizotinib groups.

PFS by IRR will be tested using the log-rank test without stratification. A stratified logrank test will be used as supportive evidence of efficacy. The supportive analysis will

be stratified by the factors used for randomization. Kaplan-Meier methods will be used to estimate the PFS survival distribution and estimates of median PFS will be provided with 95% confidence intervals.

Hazard ratio estimates will also be presented using Cox models without the stratification factors at randomization. The supportive analysis will be presented using Cox models with stratification factors at randomization included as covariates. Within the framework of Kaplan-Meier methodology, the estimates for proportions of patients with PFS durations longer than 3, 6, 12, 18, and 24 months will also be provided.

The following SAS® code (SAS Version 9.4 or more current) will be used for unstratified log-rank test for TREATMENT, as the primary efficacy analysis.

```
proc lifetest data=DATA_NAME ;
    time PFSTIME*CENSOR(0);
    strata TREATMENT;
run;
```

The following SAS® code (SAS Version 9.4 or more current) for stratified log-rank test for TREATMENT will be used as a supportive analysis.

```
proc lifetest data=DATA_NAME; time
PFSTIME*CENSOR(0); strata STRATUM /
group=TREATMENT; run;
```

Where DATA_NAME is the name of the dataset, PFSTIME is a vector containing the PFS measurement for each subject, CENSOR is its respective censoring vector (0=censored, 1=non-censored event), TREATMENT is a vector containing treatment group assignment (0=crizotinib, 1=ensartinib), and STRATUM is a vector containing the category of the randomization stratification factors.

The PFS will also be analyzed using a Cox proportional model with the randomization stratification factors as sensitivity analyses. The hazard ratio with the 95% CI and pvalue will be provided.

Cox proportional model without stratification will use the following SAS® code (SAS Version 9.4 or more current):

```
proc phreg data=DATA_NAME;
    class TREATMENT;
    model PFSTIME*CENSOR(0)=TREATMENT /risklimits ties=BRESLOW;
run;
```

Stratified Cox proportional model with randomization stratification factors as supportive analysis will use the following SAS® code (SAS Version 9.4 or more current):

```
proc phreg data=DATA_NAME; class

    TREATMENT STRATUM1-STRATUM4;

    model PFSTIME*CENSOR(0)=TREATMENT / risklimits ties=BRESLOW;
    strata STRATUM1-4;
```

run;

Where STRATUM1-STRATUM4 are the 4 stratification factors at randomization. The PFS hazard ratio less than 1.0 indicates the treatment benefit (ie, ensartinib appears to improve the PFS compared to crizotinib).

Besides the stratified log-rank test and Cox models, other sensitivity analyses for PFS will be performed to examine the robustness of the primary analysis, including

- The primary analysis results will be conducted in the mITT and PP populations;
- PFS events will be counted regardless of any missed or inadequate disease assessments prior to the event; PFS events will be counted regardless of any anticancer treatment prior to the event; PFS events will be counted if patients discontinued due to toxicity or other reasons other than documented PD.
- If significant differences in the actual stratification factor values at baseline relative the stratification factors at randomization;
- Median follow-up for overall survival and censoring patterns by treatment group will be summarized to explore possible treatment biases in patient discontinuation or loss to follow-up. Median follow-up and the censoring pattern in each treatment arm will be examined using a reverse Kaplan-Meier analysis, where censored values are events and events are censored values (Schemper 1996).

In addition, forest plots by subgroups such as stratification factors, as well as demographic and baseline patient characteristics (e.g., age (<65 and ≥65), race, gender), and possibly exploratory biomarkers will be generated displaying PFS hazard ratio and 95% CI of ensartinib versus crizotinib.

8.2.2. Analysis of Key Secondary Efficacy Variables

Among key secondary endpoints, only OS will be tested formally at 0.05 if the primary endpoints of PFS is statistically significant. Other secondary endpoints will be tested at 0.05 each and will be considered as exploratory.

OS is defined as the time in months from date of randomization to death due to any cause. Patients who are alive or lost to follow-up as of a data analysis cutoff date will be right-censored. The censoring date will be determined from the patients' date of last contact or data analysis cutoff date, whichever event occurs first. OS will be analyzed using same Kaplan-Meier methodology and Cox models used for the primary endpoint of PFS. Censoring rules for OS are described in Section 7.6. Two interim analyses of OS will be performed at the time of the interim and final analysis of the primary endpoint of PFS respectively. First interim analysis will be performed when a total of 56 deaths are expected at 75% (143/190) of maturity for PFS events by IRR. Second interim analysis will be performed when a total of 75 deaths are expected at 100% (190/190) of maturity for PFS events by IRR. The OS will be tested at alpha level of 0.0006 for first interim analysis and 0.0037 for second interim respectively, using O'Brien-Fleming Lan-DeMets alpha spending function at 2-sided alpha level of 0.05.

The final analysis for OS will be performed once approximately 145 deaths (50% of 290 subjects enrolled) have died. The median OS in the crizotinib arm is assumed to be 30 months and the expected median OS in the ensartinib treatment arm is 37.5 months, equating to an HR of 0.8. On the basis of the sample size powered for PFS, the trial will not be powered (as low as 27% power) to demonstrate a statistically significant difference in OS of this magnitude.

For CNS ORR per IRR, patients who do not have a CNS response assessment for any reason will be counted as a CNS non-responder. The denominator for the calculated proportion of CNS responders in each treatment group is the number of ITT population with CNS metastasis at baseline in that group. The proportions of CNS responders in the two treatment groups will be compared using a Chi-square test, unless some cells have <5 subjects, in which case the Fisher's exact test will be primary. A Fisher's exact test (2sided) will be presented as a supportive analysis. As supportive analysis, CNS ORR will also be calculated among subjects who have measurable CNS lesions.

CNS ORR per IRR will also be analyzed in the mITT population with CNS metastasis at baseline. For other supportive analyses, chi-square tests and stratified CMH analyses will also be performed in each population. The CMH analysis will include stratification factors used from randomization. A second CMH analysis will include only the stratification factor of Region.

The number of patients with a CR, PR, SD, PD and NE by RECIST 1.1 CNS criteria will be listed and summarized.

Two-sided 95% confidence intervals (CIs) for the proportions will be calculated using the Clopper-Pearson method. The difference between the CNS responder proportions in the two treatment groups with 2-sided 95% confidence intervals will be calculated using the Newcombe score (ie, Wilson) method (Newcombe 1998). The following SAS® code (SAS Version 9.4) will be used for the proportions estimate along with the 95% confidence interval using the Wilson method.

```
 proc freq data=DATA_NAME ;
by TREATMENT;
 tables CNS RESPONSE/binomial (CL=exact) alpha=0.05;
run;
```

The following SAS® code (SAS Version 9.4) will be used to generate 1-sided, left-tailed Fisher's exact test p-value test and the 95% confidence interval for the difference in proportions (risk difference) using the Newcombe score (aka Wilson) method:

```
 proc freq data=DATA_NAME ;
 tables TREATMENT*CNS RESPONSE/chisq riskdiff (CL=newcombe) alpha=0.05;
run;
```

The following SAS® code (SAS Version 9.4) will be used for the CMH analysis:

```
        proc freq data=DATA_NAME;
```

```
tables STRATUM*TREATMENT *CNS RESPONSE / cmh scores=modridit;
run;
```

Where DATA_NAME is the name of the dataset, TREATMENT is a vector containing treatment group assignment; RESPONSE is a vector containing the response for each subject; STRATUM is a vector containing all levels of the randomization stratification factors (or Region strata only, in the second analysis). The CNS response proportions estimates will be reported from the binomial proportion, along with 95% confidence interval.

Time to CNS progression per IRR will be analyzed using the same methods as the primary PFS analysis supported by an analysis with a competing risks model, in which non-CNS progression and death are competing risks in the analysis. See Appendix 1 for SAS code for the competing risks analysis.

Overall ORR per IRR will be analyzed using the same methods of CNS ORR per IRR.

8.2.3. Analysis of Other Secondary Efficacy Variables

Additional secondary endpoints will be analyzed for the ITT population and are:

- ORR based on investigator assessment
- Time to response based on IRR and investigator assessment
- Duration of response and disease control based on IRR and investigator assessment
- CNS Response Rate based on investigator assessment
- Time to central nervous system (CNS) progression based on c investigator assessment

ORR based on investigator assessment as well as CNS ORR based on investigator assessment will be performed using the same methods as of CNS ORR per IRR. Time to CNS progression per investigator assessment will be analyzed the same way as time to CNS progression per IRR.

For patients with a response, their duration of response will be analyzed. The same censoring rules and Kaplan-Meier methodology used for the primary analysis of PFS will be applied to duration of response, including the estimate and 95% CI of the median and 25^{th} and 75^{th} percentiles. The number of responders, the number with subsequent disease progression, and the number with censored values will be displayed as well. Responders with response durations longer than 3, 6, 12, 18, and 24 months will also be provided. No inferential testing will be performed.

8.2.4. Analysis of Exploratory Efficacy Variables

The primary HRQOL analysis will be based on the subset of patients in the ITT analysis population who complete both HRQOL questionnaires at baseline.

For the EORTC C30/LC13 QoL questionnaire, patients assess symptoms or problems experienced over the past week. EORTC C30/LC13 items will be summarized at each time point by number of non-missing responses, mean, standard deviation, median and range, including change from baseline.

The HRQOL analysis will evaluate the EORTC QLQ-C30 and QLQ-LC13 scores longitudinally using a linear mixed effects model for repeated measures, described in Appendix 11.1.1. This model, which assumes missing data are missing at random, will describe the rate of change in HRQOL scores over time for each treatment arm, taking into account the between-patient variability by incorporating each patient's individual starting point and individual rate of change. The MIXED procedure in SAS will be used with patient as the random effect; treatment arm will be defined as the fixed effect. The model also will include linear time effects (i.e., visit number) and time by treatment interaction terms. A covariance structure that follows an autoregressive (AR) process dependent only on the prior HRQOL assessment will be used (i.e., AR-1). In the case of non-convergence, other covariance structure such as unstructured (UN) will be explored. The p-value corresponding to the time by treatment interaction term in the mixed effects models will be used to assess the strength of the difference between treatment arms for the rate of change in HRQOL over time.

The Lung Cancer Symptom Scale is a QoL assessment asks patients to assess, over the last 24 hours, 6 symptoms and their effect on symptomatic distress, functional activities, and global quality of life on 9 visual analog scales. Similar to EORTC items, results and change from baseline will be summarized by time point, and mixed-effects repeated measures analysis will be performed. Analyses and inferential testing of scale scores derived from this questionnaire will be considered exploratory.

Time to deterioration (TTD) is defined in Section 5.1.3, is based on first observed deterioration. TTD for each of the items in EORTC C30/LC13 QoL questionnaire and the LCSS will be analyzed using Kaplan-Meier methodology described in Section 7.1.

8.3. Safety Analyses

The analyses of safety data (extent of exposure, adverse events, clinical laboratory results, ECG, vital signs and physical exam) will be performed on the Safety Population. Safety data will be examined on an ongoing basis while the study is being conducted.

There is a window of ±14 days for each on-treatment visit for analysis purposes. Patient assessments falling outside of the visit window will be excluded from change from baseline analysis and by visit summaries.

Terminology from version 19.0 of the Medical Dictionary for Drug Regulatory Activities (MedDRA) will be used to assign System Organ Class (SOC) and Preferred Terms classification to AEs and diseases, based on the original terms entered on the eCRF.

The incidence of treatment-emergent AEs (TEAEs) will be summarized by SOC, Preferred Terms, relationship to the study treatment, and severity. A by-patient listing will be provided for those patients who experience an SAE, including death, or experience an AE associated with early withdrawal from the study or study treatment.

8.3.1. Adverse Events

TEAEs are AEs that occur, having been absent before the first dose of study treatment, or have worsened in severity after initiating the study treatment up to 30 days from the last dose for all AEs and at any time beyond 30 days for AEs, SAEs, or deaths assessed by the investigator as treatment-related. TEAEs will be coded using MedDRA and assigned grades based on version 4.03 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE).

The number and percentage of patients reporting TEAEs and TEAEs considered related to study drug by the investigator will be tabulated by the worst CTCAE grade, system organ class, and preferred term, with an emphasis on Grade 3 and Grade 4 AEs. Similarly, the number and percentage of patients reporting treatment-emergent SAEs and drug-related SAEs will be tabulated, as well as TEAEs leading to discontinuation of study treatment. A patient reporting multiple cases of the same AE will be counted once within each system organ class and similarly counted once within each preferred term, and adverse events will be graded by worst CTCAE grade. Unless specified otherwise, the denominator for these calculations will be based on the number of patients in each treatment group who receive any amount of study treatment, irrespective of the total number of doses administered. To summarize, patient counts and percentages of treatment-emergent AEs will be summarized as follows:

- An overall summary of TEAEs (overall incidence of AEs and by relation to treatment, severity (ie, CTCAE grade) and seriousness, as well as deaths and patients with AEs leading to treatment discontinuation)
- TEAEs by SOC and preferred term
- TEAEs by preferred term
- Treatment-related TEAEs by SOC and preferred term
- Treatment-related TEAEs by preferred term
- Treatment-related SAEs by SOC and preferred term
- Treatment-related TEAEs by SOC, preferred term and grade
- Treatment-related TEAEs by preferred term and grade
- Treatment-related SAEs by SOC, preferred term and grade
- AEs leading to study drug discontinuation by SOC and preferred term
- Treatment-related AEs leading to study drug discontinuation by SOC and preferred term
- TEAEs of interest:
    - Pregnancy, abortion, birth defects/congenital anomalies
    - Clinically significant ECG abnormalities

Safety tables above will be displayed by region and overall.

A by-patient AE (including treatment-emergent) data listing including, but not limited to, verbatim term, preferred term, system organ class, CTCAE grade, and relationship to study treatment will be provided. Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study treatments, will be listed.

The clinical database will be used to summarize and list the serious adverse events (SAEs). All SAEs considered related to study drug will also be listed regardless of timeframe.

Section 7.3 describes the method that will be used to determine whether an AE is treatment-emergent when the start date of the AE is partially missing.

8.3.2. Clinical Laboratory Evaluations

Descriptive statistics will be provided for the clinical laboratory results (in SI units) by scheduled time of evaluation for the Safety Population, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be summarized for the maximum and minimum post-treatment values and the values at the End of Treatment visit.

Abnormal clinical laboratory results will be graded according to NCI CTCAE version 4.03, if applicable, and the grade will be presented in a by-patient data listing. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI CTCAE grade, will be provided for clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

Incidence rates of grade 3 or 4 ALT elevations are of particular interest and will be compared by treatment group using a 2-sided Fisher's exact test.

Data listings of all clinical laboratory data collected during the study will be presented by patient and treatment group. The original numeric and character values in addition to the results standardized in SI units will be presented in patient listings. Clinical laboratory values outside normal limits will be identified in data listings and will include flags for high and low values, as well as the investigators assessment of clinical significance.

A separate patient listing of clinical laboratory results deemed clinically significant or of Grade 3 and 4 toxicity labs will be provided.

Hematology will be ordered: hemoglobin, hematocrit, RBC, platelets, WBC, differentials (neutrophils, bands, lymphocytes, monocytes, eosinophils, basophils). Blood chemistry will be ordered: renal, liver function, electrolytes, and other. Renal tests will be ordered BUN, creatinine, uric acid. Liver function tests will be presented in the order of AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH). Electrolytes will be presented in the order of potassium, chloride, CO2, sodium, calcium, phosphorus. Other blood chemistry tests will be presented in the order of glucose (fasting recommended), triglycerides (fasting recommended), total cholesterol, HDL-cholesterol, LDL-cholesterol, total protein, albumin.

Coagulation parameters will be ordered: Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR). These data will be summarized and presented with the Hematology parameters.

Hormone tests will be presented with the Chemistry parameters. Hepatitis results from Screening will be listed along with the Chemistry data.

Urinalysis lab tests will be displayed in the order of color, turbidity, specific gravity, pH, protein, glucose, ketone, RBC, WBC, epithelial cells, bacteria, casts, crystals, bile.

Only scheduled clinical laboratory tests will be used in tables and if there are repeated clinical laboratory tests, only the first value will be used, unless there are problems with the quality of the first specimen. Clinical abnormalities will be flagged for all lab tests (ie, scheduled tests, unscheduled tests, repeated tests). Laboratory tests that are not required by the protocol (eg, investigator requested labs) will be presented as Other Blood Test listing.

Data from differentials will be presented in percentages as well as in absolute values. Lab data collected in test format (eg, color, turbidity) will be presented in listings. For any lab values comprised of a character and numeric value (eg, <XX or >XX), a value of 0 will substitute for the former, and XX will substitute for the latter for the descriptive statistics summaries.

8.3.3. Vital Signs

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation for the Safety Population, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be presented for the maximum and minimum post-treatment values and the values at the End of Treatment visit. The baseline value is defined as the last non-missing value before the initial administration of study treatment. For this protocol, vital signs include systolic/diastolic blood pressure, pulse rate and oral temperature. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at the End of Treatment visit.

For vital signs, out of range values will be identified and summarized as follows:

- Systolic BP < 80 mmHg or Systolic BP ≥ 180 mmHg
- Diastolic BP < 40 mmHg or Diastolic BP ≥ 120 mmHg
- Heart Rate < 50 bpm or Heart Rate ≥ 120 bpm
- Temp < 95 °F or Temp ≥ 100.4 °F
- Respiration Rate > 30 breaths per minute

8.3.4. ECG

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation for the Safety Population, as well as for the change from baseline, based on the readings provided by ERT. The baseline value is defined as the last non-missing value

before the initial administration of study treatment. In addition, the number and percentage of patients with ECG interval values meeting certain criteria will be tabulated (e.g., QTcF ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms) and QTcF maximum changes from baseline (>30 ms and >60 ms) over all post treatment evaluations will be summarized. ECG data will also be presented in the data listings.

8.3.5. Physical Findings

Physical examination data will be listed.

8.3.6. Dosing and Extent of Exposure

Study drug exposure and duration will be summarized by treatment group using descriptive statistics in the Safety population by cycle.

The following treatment exposure parameters will be summarized:

Total duration of treatment (months) from first dose to last dose

Average daily dose (mg) by cycle to end of treatment

Descriptive summary of compliance as percentage of scheduled dose

Categorical summary of compliance (<70%, 70-110%, >=110%)

Number of patients with dose reductions (>=1 reduction, >=2, >=3), interruptions (>=3 days, >=7, and re-escalations after previous reductions for toxicity ((>=1 re-escalation, >=2, >=3).

Absolute dose intensity, defined as cumulative total dose divided by total duration period of treatment from first to last dose in days (mg/day)

Relative dose intensity, defined as 100 x (absolute dose intensity / protocol daily dose (225 mg for ensartinib and 500 mg for crizotinib)

A patient listing of all dose modifications and/or interruptions will be provided.

8.3.7. Prior and Concomitant Medications

All medications including prescription, over-the-counter (OTC), herbal and other nutritional vitamins and/or supplements taken within 28 days of Day 1 will be recorded on the eCRF. A concomitant medication is any medication taken concurrent with study treatment (either started on or after the initial dose, or started prior but is ongoing). Prior medications are ones that are started prior to the initial dose, regardless if they are ongoing. Medications will be coded using the WHO Drug Enhanced March 2016, Format B2.

Number and percentage of patients taking prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) code and preferred term by showing frequencies and percentages and presented by treatment group.

8.3.8. Analysis of Other Safety Variables

None.

8.4. Pharmacokinetics Analyses

Plasma–concentration data from these samples will be analyzed using a population pharmacokinetic (PopPK) approach using nonlinear mixed effects modeling. A separate pharmacokinetics report, including possible exposure-response analysis, will be generated and is not in the scope of this SAP. For the CSR, PK parameters will be summarized using descriptive statistics.

8.5. Pharmacodynamic/Biomarker Analysis

Blood samples collected at specified time points will be analyzed for biomarkers. If data permit, exposure–response relationships will be explored.

Available archival tissue specimens from the tumor will be evaluated for over-expression and/or translocations of interest. Pharmacodynamic data from each assay will be listed and possible relationships between PK and PDy variables may be explored.

Biomarker data will be summarized using descriptive statistics by treatment and visit. Efficacy-biomarker data and exposure-biomarker data will be summarized and may be modeled if data permit.

9. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

None.

10. REFERENCES

Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer. 1994;30A(5):635-42.

Brookmeyer R, Crowley J. A Confidence Interval for the Median Survival Time. Biometrics 1982; 38, No. 1: 29-41

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

Fayers, P., Aaronson, N. K., Bjordal, K., Groenvold, M., Curran, D., & Bottomley, A. EORTC QLQ-C30 Scoring Manual. (3rd ed.) Brussels: European Organisation for Research and Treatment of Cancer, 2001.

ICH-E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, October 2005.

Imaging Review Charter Version 2.0 (Xcovery Protocol X396-CLI-301), MEDIAN Clinical Trial Imaging Services, 20 December 2017.

Maringwa, J.T., Quinten, C., King, M. et al. Support Care Cancer 19: 1753, 2011.

Newcombe, RG: Interval Estimation for the Difference Between Independent Proportions: Comparison of Eleven Methods. Statistics in Medicine, 17, 873–890, 1998.

O'Brien, P. C. and Fleming, T. R. (1979), "A Multiple Testing Procedure for Clinical Trials," Biometrics, 35, 549–556.

Osoba D, Rodrigues G, Myles J. et al. Interpreting the significance of changes in healthrelated quality-of-life scores. J Clin Oncol.; 16:139–44, 1998.

SAS/Stat User's Guide Version 15.1. SAS Institute, Cary NC, 2018.

Schemper M, Smith TL. A Note on Quantifying Follow-up in Studies of Failure Time. Controlled Clinical Trials 1996; 17: 343-346.

Taphoorn MJB, Stupp R, Coens C, et al. Health-related quality of life in patients with glioblastoma: a randomised controlled trial. Lancet Oncol.; 6: 937-944, 2005.

Wilson, EB: Probable Inference, the Law of Succession, and Statistical Inference. Journal of the American Statistical Association, 22, 209, 1927.

11. APPENDICES

11.1. Appendix 1 – Additional SAS Code for Analyses

11.1.1. QoL Longitudinal Analysis – Mixed-effects Model Repeated Measures

The following SAS code will be used to analyze treatment effects across visits for QoL items from QLQ-C30, QLQ-LC13 and LCSS:

```
proc mixed data=QOL method=reml;
class TREATMENT MONTH SUBJID;
  model QOL1_CFB=QOL1_BASE TREATMENT MONTH
TREATMENT*MONTH
    /
      solution ddfm=kenwardroger;    repeated MONTH/type= AR(1)
subject=SUBJID;    lsmeans TREATMENT*MONTH/slice=MONTH
diff alpha=0.05 cl;
run;
```

11.1.2. Competing Risks Analysis for CNS Progression

As supportive analysis, the time to CNS progression will be analyzed on the basis of cumulative incidence function. The probability of having a CNS progression and a nonCNS progression or death will be estimated using a cumulative incidence function for the specific event (CNS progression and Non-CNS progression/death). Death and non-CNS progression will be considered as competing events for the CNS progression cumulative incidence. Death and CNS progression will be used as competing events for the non-CNS cumulative incidence.

The cumulative incidence functions will be estimated by using the SAS macro %cumincid. A stratified Fine & Gray's model will be applied on cumulative incidence function to test the difference among treatment groups. The Fine & Gray model will be fit by the use of a weighted proportional hazard model, with the treatment group entered as the unique covariate and the stratification factors (from eCRF) used to stratify the hazard baseline function. The individual weights will be calculated with the published SAS macro %PSHREG. The following SAS code will be used to estimate the cumulative incidence functions:

```
%CUMINCID(DATA=dataset,TIME=survtime,STATUS=Status,EVENT=1,COMPETE
=2,CEN
SORED=0,STRATA=Treat, OUT=outds);
```

The parameters for the %CIF macro from SAS are as follows:

_ DATA=dataset specifies the data set to analyze.
_ TIME=Survtime specifies the time variable.
_ STATUS=Status specifies the name of the numeric variable whose values indicate whether an observation corresponds to the event of interest, the competing events, or is censored: 0 for censoring, 1 for event of interest (CNS progression), or 2 for competing risk (non-CNS progression, death)
_ EVENT=1 specifies the value for the event of interest.
_COMPETE=0 specifies the value for the competing event

_ CENSORED=0 specifies the value used to indicate censoring. Values that are specified with the STATUS=parameter rather than those specified with the EVENT= and CENSORED= parameters are for competing risks. _ STRATA=Treat requests a cumulative incidence curve for each treatment group
_OUT= outds specifies the name of the output dataset

The following SAS code will be used to fit the Fine & Gray model:
First, the individual weights will be calculated with the %PSHREG macro:

```
%PSHREG(DATA=dataset,ID=id, TIME=survtime, CENS=STATUS,
VARLIST=Treat, OUT=outds_wgt)
```

Where
_DATA=dataset specifies the data set to analyze
_ID=id specifies the subject unique identifier
_TIME=survtime specifies the time variable
_CENS=STATUS specifies the name of the numeric variable whose values indicate whether an observation corresponds to the event of interest, the competing events, or is censored
_VARLIST= Treat specifies the list of covariates to include in the model, here only the treatment variable
OUT=outds_wgt specifies the name of the output dataset

Second, a weighted PHREG procedure will be used to fit the Fine & Gray model:

```
%PHREG DATA= outds_wgt COVS(AGGREGATE) ;
MODEL (_start_,_stop_)*_censcrr_(0) = Treat / RL=PL;
WEIGHT _weight_;
ID;
STRATA strate1 strate2;
ODS OUTPUT ParameterEStimates = PE; RUN;
```

The summary table will include the number of subjects at risk, estimates of the cumulative incidence rate (%) for both treatment groups and two-sided 95% CIs. The standard error of cumulative incidence will be computed using the counting process method. The p-value coming from the Wald's test associated to the treatment variable in the Fine & Gray's model will also be displayed. Plots of the estimated cumulative incidence rate will be displayed by treatment group. All the corresponding information related to time to CNS progression as per IRR will be listed.

11.2. Appendix 2 – List of Planned Tables, Figures and Listings for Analysis

These outputs may not reflect the final outputs developed for the clinical study report. If outputs are added or removed from the analysis, or if renumbering occurs, those changes will not be made to this appendix. The final CSR numbering scheme for the outputs may be modified, as needed, but the Reference Numbers must remain unique and existing reference numbers will not be modified or be reused, even if an output is removed.

Type	CSR Number	Reference Number	For DMC * Safety ** IA	Title1	Title2	Population
Table	14.1.1.1	TREF21	*	Subject Disposition		ITT
Table	14.1.1.2	TREF22	**	Stratification Factors		ITT
Table	14.1.1.3	TREF23	**	Subject Populations for Analysis		ITT
Table	14.1.1.4	TREF24		Major Protocol Deviations by Site		ITT
Table	14.1.1.5	TREF25		Protocol Deviation by Categories		ITT
Table	14.1.2.1	TREF26	*	Demographic and Baseline Characteristics		ITT
Table	14.1.3.1	TREF28		Disease History and Prior Therapy		ITT
Table	14.1.3.2	TREF30		Medical History		ITT
Table	14.1.4.1	TREF31	**	Study Drug Exposure		Safety
Table	14.1.4.2	TREF32	**	Study Drug Modifications and Interruptions		Safety
Type	**Number**	**Number**	**** IA**	**Title1**	**Title2**	**Population**
Table	14.1.5.1	TREF33		Summary of Prior Medications		Safety

	CSR	Reference *	For DMC Safety			
Table	14.1.5.2	TREF34		Summary of Concomitant Medications		Safety
Table	14.1.5.3	TREF35		Prior and Concomitant Procedures		Safety
Table	14.1.5.4	TREF36		Concomitant Radiation Therapy		Safety
Table	14.2.1.1	TREF37	**	Progression-free Survival per IRR		ITT
Table	14.2.1.2	TREF38	**	Progression-free Survival per IRR		mITT
Table	14.2.1.3	TREF39		Progression-free Survival per IRR		Per-protocol
Table	14.2.1.4	TREF40		Progression-free Survival per IRR - Without Censoring for Missed Visits		ITT
Table	14.2.1.5	TREF42		Progression-free Survival per IRR - Actual Stratification Factor Values at Baseline		ITT
Table	14.2.1.6	TREF44		Progression-free Survival per Investigator		ITT
Table	14.2.2.1	TREF46	**	Overall Survival		ITT
Table	14.2.2.2	TREF47	**	Overall Survival		mITT
Table	14.2.2.3	TREF48		Overall Survival		Per-protocol
Table	14.2.2.4	TREF49		New Anti-cancer Therapy		ITT
Type	**Number**	**Number**	**** IA**	**Title1**	**Title2**	**Population**
Table	14.2.3.1	TREF51	**	Best Overall Response per IRR		ITT

	CSR	Reference *	For DMC Safety			
Table	14.2.3.2	TREF54		Time to Response per IRR	Patients with Response of CR or PR	ITT
Table	14.2.3.3	TREF56		Duration of Response per IRR	Patients with Response of CR or PR	ITT
Table	14.2.3.4	TREF58	**	CNS Response per IRR	Patients with CNS Disease at Baseline	ITT
Table	14.2.3.5	TREF60	**	Time to CNS Progression per IRR	Patients with CNS Disease	ITT
Table	14.2.3.6	TREF62		Time to CNS Progression with Competing Risks per IRR	Patients with CNS Disease	ITT
Table	14.2.3.7	TREF119		Best Overall Response per Investigator	Patients with Measurable Disease	ITT
Table	14.2.3.8	TREF66		Time to Response per Investigator	Patients with Response of CR or PR	ITT
Table	14.2.3.8	TREF68		Duration of Response per Investigator	Patients with Response of CR or PR	ITT
Table	14.2.3.10	TREF70		CNS Response per Investigator	Patients with CNS Disease	ITT
Table	14.2.3.11	TREF72		Time to CNS Progression per Investigator	Patients with CNS Disease	ITT
Table	14.2.3.12	TREF74		Time to CNS Progression with Competing Risks per Investigator	Patients with CNS Disease	ITT

Type	**Number**	**Number**	**** IA**	**Title1**	**Title2**	**Population**

	CSR	Reference	For DMC * Safety		
Table	14.2.4.1	TREF76	**	Summary and Change from Baseline of EORTC-C30/LC13 Questionnaire Items by Visit	ITT
Table	14.2.4.2	TREF78		Time to Deterioration in EORTCC30/LC13 Questionnaire Items	ITT
Table	14.2.4.3	TREF80	**	Longitudinal Analysis of EORTCC30/LC13 Questionnaire Items	ITT
Table	14.2.4.4	TREF82	**	Summary and Change from Baseline of Lung Cancer Symptom Scale Items by Visit	ITT
Table	14.2.4.5	TREF84		Time to Deterioration in Lung Cancer Symptom Scale Items	ITT
Table	14.2.4.6	TREF86	**	Longitudinal Analysis of Lung Cancer Symptom Scale Items	ITT
Table	14.2.5.1	TREF88		Progression-free Survival per IRR by Subgroups	ITT
Table	14.2.5.2	TREF89		Overall Survival per IRR by Subgroups	ITT
Table	14.2.5.3	TREF90		Best Overall Response per IRR by Subgroups	ITT

			For DMC			
	CSR	Reference *	Safety			
				Occurring in ≥ 10% of Ensartinib Patients by System Organ Class, Preferred Term, and Maximum CTCAE Grade		
Table	14.3.1.5	TREF96		Treatment-Emergent Adverse Events with Grade 3 or Higher by System Organ Class, Preferred Term, and Maximum CTCAE Grade		Safety
Table	14.3.1.6	TREF98	*	Treatment-emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum CTCAE Grade		Safety
Type	**Number**	**Number**	**** IA**	**Title1**	**Title2**	**Population**

	CSR	Reference *	For DMC Safety			
Table	14.3.1.1	TREF91	*	Overall Summary of Treatmentemergent Adverse Events		Safety
Table	14.3.1.2	TREF93	*	Overall Summary of Treatmentemergent Adverse Events by Region (Asia vs ROW)		Safety
Table	14.3.1.3	TREF94	*	Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum CTCAE Grade		Safety
Table	14.3.1.4	TREF95		Treatment-Emergent Adverse Events		Safety
Type	**Number**	**Number**	**** IA**	**Title1**	**Title2**	**Population**
Table	14.3.1.7	TREF100	*	Serious Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum CTCAE Grade		Safety
Table	14.3.1.8	TREF101	*	Serious Treatment-emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum CTCAE Grade		Safety
Table	14.3.1.9	TREF102		Treatment-Emergent Adverse Events Leading to Dose Reduction by System Organ Class, Preferred Term, and Maximum CTCAE Grade		Safety

	CSR	Reference *	For DMC Safety			
Table	14.3.1.10	TREF103		Treatment-Emergent Adverse Events Leading to Dose Delay by System Organ Class, Preferred Term, and Maximum CTCAE Grade		Safety
Table	14.3.1.11	TREF104		Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class, Preferred Term, and Maximum CTCAE Grade		Safety
Table	14.3.1.12	TREF105		Deaths		Safety
Type	**Number**	**Number**	**** IA**	**Title1**	**Title2**	**Population**
Table	14.3.1.13	TREF106	*	Selected Treatment-emergent Adverse Events by System Organ Class, Preferred Term, Maximum CTCAE Grade and Region (Asia vs ROW)		Safety
Table	14.3.1.14	TREF121	*	Summary of Subjects with Treatmentemergent Adverse Events (TEAEs), by Preferred Term and Severity		Safety
Table	14.3.2.1	TREF107	*	Hematology Value Shift from Baseline to Maximum on Treatment CTCAE Grade		Safety
Table	14.3.2.2	TREF108	*	Hematology Value Change from Baseline by Visit		Safety

	CSR	Reference *	For DMC Safety			
Table	14.3.2.3	TREF109	*	Chemistry Value Shift from Baseline to Maximum on Treatment CTCAE Grade		Safety
Table	14.3.2.4	TREF110	*	Chemistry Value Change from Baseline by Visit		Safety
Table	14.3.2.5	TREF111	*	Coagulation Value Shift from Baseline to Maximum on Treatment CTCAE Grade		Safety
Table	14.3.2.6	TREF112	*	Coagulation Value Change from Baseline by Visit		Safety
Type	**Number**	**Number**	**** IA**	**Title1**	**Title2**	**Population**
Table	14.3.2.7	TREF113	*	Urinalysis Value Change from Baseline by Visit		Safety
Table	14.3.2.8	TREF114	*	Vital Signs Change from Baseline by Visit		Safety
Table	14.3.3.1	TREF115	*	ECG Parameters by Visit		Safety
Table	14.3.3.2	TREF116	*	Prolongation of QTcF		Safety
Table	14.3.4	TREF117		ECOG Performance Status Shifts from Baseline		Safety
Table	14.4.1	TREF118		Summary of PK Parameters	Patients with PK data	Safety

	CSR	Reference *	For DMC Safety			
Table	14.4.2	TREF119		Summary of Biomarker Data by Visit	Patients with biomarker data	Safety
Figure	14.2.1.1	FREF11	**	Kaplan-Meier Plot for Progression-free Survival per IRR		ITT
Figure	14.2.1.2	FREF13		Waterfall Plot for Best Change from Baseline in Target Lesions per IRR		ITT
Figure	14.2.1.3	FREF15		Reverse Kaplan-Meier Plot for Progression-free Survival per IRR		ITT
Figure	14.2.1.4	FREF17		Forest Plot for Progression-free Survival per IRR by Subgroups		ITT
Figure	14.3.1.2	FREF27		Kaplan-Meier Plot for Time to CNS Progression with Competing Risks per IRR	Patients with CNS Disease	ITT
Figure	14.3.1.3	FREF28		Kaplan-Meier Plot for Time to CNS	Patients with CNS	mITT

Type	CSR Number	Reference Number	For DMC * Safety ** IA	Title1	Title2	Population
Figure	14.2.2.1	FREF19	**	Kaplan-Meier Plot for Overall Survival		ITT
Figure	14.2.2.2	FREF20	**	Kaplan-Meier Plot for Overall Survival		mITT
Figure	14.2.2.3	FREF21		Reverse Kaplan-Meier Plot for Overall Survival		ITT
Figure	14.2.2.4	FREF23		Forest Plot for Overall Survival by Subgroups		ITT
Figure	14.3.1.1	FREF25		Kaplan-Meier Plot for Time to CNS Progression per IRR	Patients with CNS Disease	ITT
				Progression with Competing Risks per IRR	Disease	
Figure	14.4.1	FREF29	*	Hematology Tests – Bar Charts by CTCAE Grade		Safety
Figure	14.4.2	FREF30	*	Chemistry Tests – Bar Charts by CTCAE Grade		Safety
Figure	14.4.3	FREF31	*	Liver Function Test: Alanine Aminotransferase (ALT) Scatterplot		Safety

Type	CSR Number	Reference Number	For DMC * Safety ** IA	Title1	Title2	Population
Figure	14.4.4	FREF32	*	Liver Function Test: Alkaline Phosphatase Scatterplot		Safety
Figure	14.4.5	FREF33	*	Liver Function Test: Aspartate Aminotransferase (AST) Scatterplot		Safety
Figure	14.4.6	FREF34	*	Liver Function Test: Bilirubin Scatterplot		Safety
Figure	14.4.7	FREF35	*	Hepatic and Renal Chemistry Tests by Region (Asia vs ROW) – Bar Charts by CTCAE Grade		Safety
Listing	16.2.1	LREF11		Disposition		ITT
Listing	16.2.2.1	LREF12		Protocol Deviations		ITT
Listing	16.2.2.2	LREF13		Inclusion/Exclusion Criteria		ITT
Listing	16.2.2.3	LREF14		Stratification Factors (Planned and Actual Stratification)		ITT
Listing	16.2.2.4	LREF15		Informed Consent		ITT
Listing	16.2.3	LREF64		Analysis Population		ITT
Listing	16.2.4.1	LREF16		Demographics and Baseline Characteristics		ITT
Listing	16.2.4.2	LREF17		Medical History		ITT

	CSR	Reference *	For DMC Safety			
Listing	16.2.4.3	LREF18		Disease Characteristics		ITT

Type	Number	Number	** IA	Title1	Title2	Population
Listing	16.2.4.4	LREF19		Prior Cancer Systemic Therapy		ITT
Listing	16.2.4.5	LREF20		Prior Cancer-Related Surgeries		ITT
Listing	16.2.4.6	LREF21		Prior Radiotherapy		ITT
Listing	16.2.4.7	LREF22		Concomitant Medications		ITT
Listing	16.2.4.8	LREF23		Concomitant Procedures		ITT
Listing	16.2.5.1	LREF24		Ensartinib Administration		Safety
Listing	16.2.5.2	LREF25		Crizotinib Administration		Safety
Listing	16.2.6.1	LREF26		Target Lesion Assessments - IRR		ITT
Listing	16.2.6.2	LREF27		Target Lesion Assessments - Investigator		ITT
Listing	16.2.6.3	LREF28		Non-Target Lesion Assessments - IRR		ITT
Listing	16.2.6.4	LREF29		Non-Target Lesion Assessments - Investigator		ITT
Listing	16.2.6.5	LREF30		New Lesions - IRR		ITT
Listing	16.2.6.6	LREF31		New Lesions - Investigator		ITT
Listing	16.2.6.7	LREF32	**	RECIST Response - IRR		ITT

	CSR	Reference *	For DMC Safety			
Listing	16.2.6.8	LREF33		RECIST Response - Investigator		ITT
Type	**Number**	**Number**	**** IA**	**Title1**	**Title2**	**Population**
Listing	16.2.6.9	LREF34	**	Time to Event Parameters - IRR		ITT
Listing	16.2.6.10	LREF35		Time to Event Parameters - Investigator		ITT
Listing	16.2.6.11	LREF36		CNS Response Parameters - IRR		ITT
Listing	16.2.6.12	LREF37		CNS Response Parameters - Investigator		ITT
Listing	16.2.7.1	LREF38		Adverse Events Sorted by Patient and Onset Date		Safety
Listing	16.2.7.2	LREF39	*	Grade 3 or Higher Study Drug-related Adverse Events		Safety
Listing	16.2.7.3	LREF40	*	Serious Treatment-Emergent Adverse Events		Safety
Listing	16.2.7.4	LREF41	*	Treatment-Emergent Adverse Events Lead to Dose Reduction		Safety
Listing	16.2.7.5	LREF42		Treatment-Emergent Adverse Events Lead to Dose Delay		Safety
Listing	16.2.7.6	LREF43	*	Treatment-Emergent Adverse Events Lead to Adverse Events Leading to Treatment Discontinuation		Safety

	CSR	Reference	* For DMC Safety			
Listing	16.2.7.7	LREF44		Treatment-Emergent Adverse Events Lead to Death		Safety

Type	Number	Number	** IA	Title1	Title2	Population
Listing	16.2.7.8	LREF45	*	Deaths		Safety
Listing	16.2.8.1	LREF46		Hematology Tests		Safety
Listing	16.2.8.2	LREF47	*	Hematology Tests with CTCAE Grade 3 or 4 Toxicity		Safety
Listing	16.2.8.3	LREF48		Chemistry Tests		Safety
Listing	16.2.8.4	LREF49	*	Chemistry Tests with CTCAE Grade 3 or 4 Toxicity		Safety
Listing	16.2.8.5	LREF50	*	Creatinine Tests in Subjects with CTCAE Grade 2 or Higher Creatinine		Safety
Listing	16.2.8.6	LREF51		Coagulation Tests		Safety
Listing	16.2.8.7	LREF52	*	Coagulation Tests with CTCAE Grade 3 or 4 Toxicity		Safety
Listing	16.2.8.8	LREF53		Urinalysis		Safety
Listing	16.2.9	LREF54		Vital Signs		Safety
Listing	16.2.10	LREF55	*	ECG QTcF Findings		Safety
Listing	16.2.11	LREF56		Physical Exam		Safety

	CSR	Reference *	For DMC Safety			
Listing	16.2.12	LREF57		ECOG Scores		Safety
Listing	16.2.13	LREF58		Pregnancy Tests		Safety

Type	**Number**	**Number**	**** IA**	**Title1**	**Title2**	**Population**
Listing	16.2.14.1	LREF59		EORTC QLQ-C30/LC13 Questionnaire		ITT
Listing	16.2.14.2	LREF60		Lung Cancer Symptom Scale Questionnaire		ITT
Listing	16.2.15.1	LREF61		Response & Survival Follow-up		ITT
Listing	16.2.15.2	LREF62		Anti-Cancer Therapy		ITT
Listing	16.2.16	LREF63		PK Parameters		Safety