X396-CLI-101

Phase I/II, First-in-Human, Dose-Escalation Study of X-396 in Patients with Advanced Solid Tumors and Expansion Phase in Patients with ALK+ Non-Small Cell Lung Cancer

PROTOCOL NUMBER:	X396-CLI-101
TRIAL DRUG:	X-396 (ensartinib)
IND NUMBER:	111,695
EUDRA-CT #:	2015-003191-80
SPONSOR:	Xcovery Holdings, Inc. 11780 U.S. Highway One, Suite 202 Palm Beach Gardens, FL 33408
SPONSOR REPRESENTATIVE:	Chris Liang, Ph.D.
MEDICAL MONITOR:	Jon Gockerman, M.D. Novella Clinical, Inc. jgockerman@novellaclinical.com
ORIGINAL PROTOCOL DATE:	05 January 2012

AMENDMENT NUMBER: 1		**AMENDMENT DATE:**	23 March 2012
AMENDMENT NUMBER: 2		**AMENDMENT DATE:**	30 April 2012
AMENDMENT NUMBER: 3		**AMENDMENT DATE:**	06 September 2012
AMENDMENT NUMBER: 4		**AMENDMENT DATE:**	04 November 2013
AMENDMENT NUMBER: 5		**AMENDMENT DATE:**	02 July 2014
AMENDMENT NUMBER: 6		**AMENDMENT DATE:**	16 March 2015
AMENDMENT NUMBER: 7		**AMENDMENT DATE:**	11 September 2015
AMENDMENT NUMBER: 8		**AMENDMENT DATE:**	25 May 2016
AMENDMENT NUMBER: 9		**AMENDMENT DATE:**	29 January 2018

Principal Investigator Signature Form

TITLE: Phase I/II, First-in-Human, Dose-Escalation Study of X-396 in Patients with Advanced Solid Tumors and Expansion Phase in Patients with ALK+ Non-Small Cell Lung Cancer

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PRINCIPAL INVESTIGATOR COMMITMENT:

I have fully discussed the objectives of this trial and the contents of this protocol with the Sponsor and their representatives.

I understand that the information in this protocol is confidential and may not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent once formal and written IRB/EC approval is obtained.

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that this clinical trial shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)
- Ethical principles that have their origins in the Declaration of Helsinki
- Food and Drug Administration (FDA) Code of Federal Regulation (CFR):
  - Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects
  - Title 21CFR Part 54, Financial Disclosure by Clinical Investigators
  - Title 21CFR Part 56, Institutional Review Boards
  - Title 21CFR Part 312, Investigational New Drug Application
  - Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)

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

Clinical Trial Signature Approval Page

TITLE: **Phase I/II, First-in-Human, Dose-Escalation Study of X-396 in Patients with Advanced Solid Tumors and Expansion Phase in Patients with ALK+ Non-Small Cell Lung Cancer**

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JON P. GOCKERMAN	[signature]	15 FEB 2018
Medical Monitor (Name Printed)	**Medical Monitor Signature**	**Date**

Chris Liang	Chris Liang	Feb. 14, 2018
Sponsor Representative (Name Printed or Typed)	**Sponsor Representative Signature**	**Date**

History of Trial Amendments

TITLE: Phase I/II, First-in-Human, Dose-Escalation Study of X-396 in Patients with Advanced Solid Tumors and Expansion Phase in Patients with ALK+ Non-Small Cell Lung Cancer

Amendment # Amendment Date	**Revision(s) Made**
Amendment 1 23 March 2012	• Accelerated titration Synopsis and Section 7.1 and 7.1.1 have been modified to require switch to 3+3 escalation scheme when 1 patient experiences ≥ Grade 2 drug-related toxicity • Physical examination expanded to specify whole body skin examination in Appendix E. • Section 8 Dose Modification language and Section 14 Discontinuation of Trial Treatment revised removing all patients from trial treatment requiring a hold ≥4 weeks due to treatment-related toxicity. • Correction made to Section 1.1.1.4 X-396 Overall Risk Assessment
Amendment 2 30 April 2012	• Blood specimen collection (1 EDTA tube) for pharmacogenetic testing to be obtained. Section 2.3 Exploratory Objectives, Section 3.2 Secondary Endpoints, Section 9.8, and Appendix E and list of abbreviations updated accordingly. • Testosterone monitoring will be performed in male patients. Section 9.6.2.4 and Appendix E updated accordingly. • PAXgene tissue collection removed from Section 9.9.1 and Appendix E. • ALK will be confirmed by MolecularMD. Section 9.9.1, Section 13.2.3 Tumor Response, and Appendix E revised accordingly. • MET analysis changed to IHC from FISH. Inclusion criterion #11, Section 9.9.1 and Appendix E revised accordingly. • Ophthalmology exam expanded to also include history, symptoms, medications, eye movements, visual field, and funduscopic exam in Section 9.6.3.2 and Appendix E. • Protocol changes have been carried through the Synopsis.
Amendment 3 06 September 2012	• A potential safety concern has prompted additional monitoring of active and newly enrolled patients. An SAE reporting a patient who received 1 cycle of treatment with X-396 was diagnosed with thrombotic microangiopathy (TMA). The relationship to X-396 has not been ruled out. Twice weekly hematology and clinically chemistries collected during Cycle 1 and on Days 1, 8 and 15 of Cycle 2 until the Medical Monitor determines that this is no longer required. The following sections have been created or modified: Section 1.1.1.4, Section 9.6 and Appendix E. • Section 9.9.1 has been revised to clearly state that fresh tumor biopsy material is preferred during pre-treatment for the dose escalation portion of the study but not a requirement. The requirement for the pre-treatment fresh tumor biopsy during the expansion phase has not been changed.

History of Trial Amendments

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Amendment # Amendment Date	**Revision(s) Made**
Amendment 3 (*continued*) 06 September 2012	• Section 10.1 has been clarified to document that the size of the HDPE bottle in which X-396 is dispensed to patients is not required to be 150cc. There is no mandated requirement. Sites may repackage the investigational product according to local standards. • Appendix E: Superscript p has been revised to harmonize with the changes made in Section 9.9.1. Additional monitoring noted above and new superscript v have been added. • Minor clarifications were also made to various sections.
Amendment 4 04 November 2013	• Section 1.1.1.4 and Appendix E amended to update information about hematology and chemistry collection. Section 1.1.1.4 was also updated to include information about 1 report each of drug-related fluid overload and erythematous, pruritic, peeling skin. • Inclusion criterion #1, Synopsis, Section 5.1, and Section 7.1.5 revised to allow patients in both the dose escalation and dose expansion portions of the study to have received prior crizotinib and/or second generation ALK tyrosine kinase inhibitors (TKIs). • Inclusion criterion #5, Synopsis and Section 5.1 revised to allow up to 10 ALK-positive patients with small (up to 1 cm) untreated central nervous system lesions to be treated in the dose expansion or previously completed dose escalation cohorts if the lesions have been stable for > 4 weeks and the patients are asymptomatic and do not require escalating doses of systemic corticosteroids. • Exclusion criterion #2, Synopsis, Section 5.2 revised to exclude use of targeted drug within 21 days or 5 half-lives (minimum of 10 days) prior to the first dose of X-396 with the exception of crizotinib, for which a 5 day window between termination of crizotinib and X-396 is allowed. • Section 7 revised for the potential to explore dosing with food and also to allow patients taking X-396 under fasting conditions to take X-396 with food if deemed appropriated by the investigator and Medical Monitor. • Section 7.1.2 and Synopsis revised to permit intra-patient dose escalation. • Section 7.2 revised to allow radiation therapy (without specifying the type) for 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. • Added paragraph to Section 8 to explain intra-patient dose escalation. • Minor clarifications were also made to various sections.

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Amendment # Amendment Date	**Revision(s) Made**
Amendment 5 02 July 2014	• List of Abbreviations was updated. • Section 1.1.1.4 X-396 Overall Risk Assessment has been updated to include information on X-396 as well as information from the crizotinib label and information from the ceritinib label. • The number of patients planned to be enrolled in this study has been increased from 60 to up to 100. This has been added to Section 4 Trial Design, Section 13.1 Statistical Design, Section 13.3.2 Power and Sample Size Determination, and the Synopsis. The anticipated study duration and number of sites has also been updated in Section 4 and/or the Synopsis. • Section 5.1 Inclusion criterion #1 and the Synopsis have been revised to delete the phrase "As long as the therapy was tolerated" in reference to prior ALK TKIs. • Section 5.1 Inclusion criterion #5 and the Synopsis have been revised with respect to patients with previously treated and untreated CNS metastases. In addition, up to 5 patients with leptomeningeal disease are eligible in the expansion cohort. • Section 5.1 Inclusion criteria #9 and #10 and the Synopsis have been revised to add an exception for patients in the CNS metastases and leptomeningeal disease cohorts. • Section 5.1. Inclusion criterion #11 and the Synopsis have been revised to note that patients in the expansion cohort phase must have non-small cell lung cancer and the descriptions about MET testing were deleted. • Section 5.2 Exclusion criterion #2 and Synopsis revised to add ceritinib to the crizotinib exception allowing for a minimum for 5 days between termination of that agent and the start of study medication. • Exclusion criterion #12 and Synopsis reworded to add known hepatitis C. • Exclusion criteria and Synopsis revised to delete previous exclusion criterion #13 about patients that had previously poorly tolerated an ALK or MET inhibitor. • Section 7.1.5 Expansion Cohort Phase and Synopsis have been modified. At a dose at or below the MTD, the following cohorts for NSCLC patients with ALK genomic alterations will be included: patients that are ALK TKI-naïve, patients that progressed on prior crizotinib and have not received other ALK TKIs, patients that have progressed on one 2nd generation ALK TKI, patients with CNS metastases, and patients with leptomeningeal disease. The previous cohort for patients that are ALK- and MET-negative has been removed. • Section 8 Dose Modifications criteria for intra-patient dose escalation updated to those who have not experienced ≥ Grade 1 related toxicity or required a dose reduction or interruption due to drug-related toxicity.

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Amendment # Amendment Date	**Revision(s) Made**
Amendment 5 (*continued*) 02 July 2014	• Section 9.9.1 Assessment of Tumor Tissue Samples and Appendix E Schedule of Assessments modified to add an optional assessment at the time of disease progression. Statement also added to Section 9.9.1 that MET testing will also be performed on fresh biopsy samples and the definition for MET positivity was removed. • Section 10.1 Labeling, Packaging, and Supply revised to add 30-count bottles as well as the 100-count bottles. • Section 11 Response Evaluations and Measurements was modified to include information specific to CNS metastases. • Section 13.2.3 Tumor Response modified based on the changes to the Expansion Cohort Phase. PFS also added as one of the endpoints. • Appendix E Schedule of Assessments- footnotes for brain MRI and fresh biopsies were updated, based on changes noted elsewhere in the protocol.
Amendment 6 16 March 2015	• Title updated to note that with the expansion cohort phase, this is now considered a Phase I/II study, and that the expansion phase is specifically for patients with ALK+ NSCLC. This was previously updated in an Administrative Letter. Note that the change to Phase I/II also occurs in some other sections of the protocol, including the Synopsis. • Synopsis: The number of sites was increased to up to 24 sites. • Synopsis and throughout the document, reference to, and contact information for, Novella, the new CRO, including the new Medical Monitor and Safety Department, has been added. • Section 1.1.1.4 X-396 Overall Risk Assessment was updated for X-396 and for revised labeling for crizotinib. • Section 5.1 Inclusion Criteria and Synopsis, Inclusion Criterion 1: Added to this criterion what had been Inclusion Criterion 11, requiring that patients have NSCLC that is ALK+ by FISH to be eligible for the expansion cohort phase, and deleted what had been Inclusion Criterion 11. • Section 5.1 Inclusion Criteria and Synopsis, Inclusion Criterion 5: Added that CNS lesions that have received SRS cannot be used as target lesions. For patients with leptomeningeal disease, changed to indicate that they do not have to be asymptomatic.

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Amendment # Amendment Date	**Revision(s) Made**
Amendment 6 ***(continued)*** 16 March 2015	• Section 5.1 Inclusion Criteria and Synopsis: Inclusion Criterion 9 was clarified to indicate that patients in the CNS cohort of the expansion phase must have at least 1 CNS target lesion, and for the leptomeningeal disease cohort, patients must have positive gadolinium uptake on MRI of the spine and/or brain, with neurologic findings, or tumor cells in CSF. • Section 5.1 Inclusion Criteria and Synopsis: Inclusion Criterion 10 was clarified to indicate that for patients in the leptomeningeal disease cohort, CSF should be obtained for cytology. • Section 5.2 Exclusion Criteria and Synopsis: Exclusion Criterion 2 was clarified, with alopecia being added as an exception to the need to recover to Grade 1 or less from prior therapy. • Section 7 Administration of X-396: In the expansion cohort portion of the study, approximately half of the patients will be told to take the study drug with food and half without food in Cycle 1, after which they can decide whether to take the study drug with or without food. • Section 7.1.5 and Synopsis: Added that 225 mg is the dose to be evaluated in the expansion cohort phase. Also clarified that a previously treated CNS lesion must be growing and at least 4 weeks post whole brain radiation therapy to be considered a CNS target lesion. Also added that for the leptomeningeal disease cohort, these patients do not have to be asymptomatic, and diagnosis must be by imaging along with neurologic signs/symptoms, or by tumor cells in the CSF. • Section 8 Dose Modification: Added the dose levels for the expansion cohort phase (225 mg as the starting dose, and 200 mg and 100 mg as dose levels -1 and -2, respectively, if dose reductions are necessary). • Sections 8.1 and 8.2 Dose Modifications Due to Hematologic and Non-Hematologic Toxicity: Added footnote referring to the table showing the dose levels for the expansion cohort phase. • Section 8.2 Dose Modifications for Non-Hematologic Toxicities: Added information about rashes related to X-396, including additional recommendations for treatment. • Section 9.6.5 Efficacy Assessments: CSF was added for patients in the leptomeningeal disease cohort, and an MRI at Cycle 2 Day 1 was added for these patients. • Section 9.7 PK Assessments and Appendix E Schedule of Assessments: These were modified to have a section for the dose escalation portion and the expansion cohort phase. For the latter, PK assessments are to be obtained from as many patients as possible. For those patients that will have PK samples taken, sparse PK sampling was added for those patients that can't have full PK sampling.

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Amendment # Amendment Date	**Revision(s) Made**
Amendment 6 ***(continued)*** 16 March 2015	• Section 9.9.1 Assessment of Tumor Tissue Samples: Requirements were clarified, and timing for the baseline biopsy was changed to indicate that a biopsy that had been obtained within 60 days prior to the start of treatment may be utilized for the pre-treatment biopsy if no other anticancer therapy was given after the biopsy and before the start of study treatment. In addition, CSF was added for patients in the leptomeningeal disease cohort. • Section 9.9.3 Skin Biopsies and Appendix E: A section was added to note that a skin biopsy may be obtained for patients that develop a rash thought to be related to X-396. • Section 11 Response Evaluations and Measurements: Added details specific to evaluating CNS lesions and leptomeningeal disease, and separated these out from the information for systemic disease. • Sections 12.4 Protocol-Defined Events of Special Interest and 14.1 Pregnancy: Added information to indicate that if pregnancy occurs in the partner of a male patient, the pregnancy form should be completed. • Section 13.2.3 Tumor Response: CNS response rate and time to CNS progression were added, as was clarification that analyses will also be done for the expansion cohorts. • Appendix E Schedule of Assessments: Timing of ECGs was clarified for patients not having full PK collections, MRI of spine in addition to brain and CSF were added for leptomeningeal disease, and neurologic exam was added to physical exam for patients with CNS metastases or leptomeningeal disease. • Minor clarifications/corrections were made to various parts of the document.
Amendment 7 11 September 2015	• Synopsis, Section 4, and Section 13.1 updated to allow study enrollment to expand globally for the expansion phase of the study and the number of sites was increased from 24 to 50 to allow for this expansion. • Inclusion criterion #1, Synopsis and Section 5.1, revised to allow enrollment based on local ALK testing by IHC. For the expanded cohort portion, ALK status will be confirmed centrally by either FISH or IHC. • Inclusion criterion #4, Synopsis and Section 5.1, and Section 7.1.3 Dose-Limiting Toxicity, SI units added because of global participation. • Inclusion criterion #10, Synopsis, and Section 5.1, revised to allow for possibility of enrollment based on ALK results from prior tissue specimens where ALK status could not be confirmed from fresh biopsy because of insufficient tissue/inadequate sample.

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Amendment # Amendment Date	**Revision(s) Made**
Amendment 7 ***(continued)*** 11 September 2015	• In Section 7.1.5 Expansion Cohort Phase revised to allow patients who have progressed on more than one prior 2nd generation ALK TKI to be included in the 2nd generation ALK TKI cohort. • Section 8.2.1, Specific Recommendations for Rash, minor revision to wording to encourage biopsy. • Section 9.9.1 Assessment of Tumor Tissue Samples, has been updated to clarify that enrollment can also be based on local ALK testing by IHC and that central confirmation can also be by IHC, and definition for ALK positivity by IHC was added. This section was also revised to be consistent with the changes made to Inclusion Criterion #10. • Section 9.9.3 Skin Biopsies revised to include photos of rashes in order to develop a better understanding of the rash. • Section 10.1 Labeling, Packaging, and Supply was revised to provide global language for how study drug is packaged and will be dispensed to patients. • Section 13.2.3 Tumor Response, clarification that patients in the expansion cohort phase may be deemed evaluable based on local ALK results if there are concerns about the accuracy or adequacy of the central read specimen. • Section 14 Discontinuation from Trial Treatment, clarified to allow patients with disease progression who are doing well clinically to remain on study treatment if the investigator and Medical Monitor agree that it is in the patient's best interest. • Section 17.5.1 Patient Confidentiality, was revised to allow for global confidentiality requirments as well as US. • Appendix E Schedule of Assessments: added smoking history to Medical history; digital photos of rash included; and clarified information about prior tissue samples to be consistent with Inclusion Criterion #10. • Language throughout protocol was amended to include global regulatory/ competent authorities and add Ethics Committee (EC). • In addition, minor clarifications and editorial changes were also made to various sections.
Amendment 8 25 May 2016	• Synopsis, Section 4 Trial Design, Section 13.1 Statistical Design, Section 13.3.2 Power and Sample Size Determination were revised to increase the number of patients from up to 100 to up to 150.

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Amendment # Amendment Date	**Revision(s) Made**
Amendment 8 ***(continued)*** 25 May 2016	• Synopsis Trial Population section was clarified to note that the population in the expansion cohort phase is patients with ALK+ non-small cell lung cancer. • Synopsis, Section 7.1.3 Dose-Limiting Toxicity was modified to clarify that the DLT definition applies just to the dose escalation phase. • Synopsis, Section 7.1.5 was revised to increase the number of patients in the expansion cohort phase to up to 110 patients, with up to 30 patients each in the following cohorts: prior crizotinib and no other ALK TKI, patients that have progressed on one or more 2nd generation ALK TKIs (and, with Amendment 8, patients in the latter cohort must have progressed on prior alectinib), and patients with CNS metastases. Also, with Amendment 8, the ALK TKI-naïve cohort will be closed. • Synopsis, Section 5.1 Inclusion Criterion #1 was clarified to note that patients that are ALK TKI-naïve may agree to participate and, with Amendment 8, patients that have received a prior 2nd generation ALK TKI must have progressed on alectinib. • Synopsis, Section 5.2 Exclusion Criterion #2 was revised to note that the 5-day window applies to other ALK TKIs, not just prior crizotinib and ceritinib. • Synopsis, Section 5.2 Exclusion Criterion #3, the words "limited palliative" were deleted with respect to radiation, and "focal" was added. • Synopsis, Section 5.2 Exclusion Criterion #7 pertaining to drugs with a risk of causing QT prolongation or Torsades de Pointes was deleted (see also the resulting changes to the Concomitant Medications sections of the protocol noted below) and the subsequent exclusion criteria were renumbered. • Synopsis, Section 13.3.2 Power and Sample Size Determination was revised to include the rationale for the increase in sample size up to 30 patients in 3 of the expansion cohorts. • Section 1.1.1.4 X-396 Overall Risk Assessment was updated and clarified to include more recent data for X-396 and for other ALK TKIs. • Section 7.2 Supportive Care was clarified with additional wording about the use of supportive care. • Section 7.4.1 Prohibited Concomitant Medications was revised to remove wording about the use of medications that may cause QT prolongation or Torsades de Pointes and Section 7.4.2 Concomitant Medications to Be Used with Caution was added to note that concomitant medications with a known risk of Torsades de Pointes should be used with caution. • Section 8 Dose Modification was revised to note circumstances under which a dose that had been reduced may be escalated back up to a prior dose level.

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Amendment # Amendment Date	**Revision(s) Made**
Amendment 8 ***(continued)*** 25 May 2016	• Section 8 Dose Modification changed the 2nd dose reduction level from 100 mg qd to 150 mg qd. • Sections 8.1 Dose Modification Due to Hematologic Toxicity and 8.2 Dose Modification Due to Non-Hematologic Toxicity were modified by adding "related" or "drug-related" in several places for clarification. • Section 8.2.1 Specific Recommendations for Rash was modified to include updated information on rashes observed to date with X-396 and to note that pictures may be obtained. Section 9.6.1 Additional Safety Monitoring was deleted to avoid confusion, since it no longer applies. • Section 9.6.3.5 Urinalysis and Appendix E Schedule of Assessments were modified to note that other appropriate methods besides urine dipstick may be used. • Section 9.7 Pharmacokinetic Assessments was modified to change the word "random" to "unscheduled". • Section 9.9.1 Assessment of Tumor Tissue Samples and Appendix E Schedule of Assessments were revised, changing the central assessments from being done at MolecularMD to just noting that these would be done centrally. • Section 14 Discontinuation from Trial Treatment was clarified to note that for situations where a patient has progressive disease on study but it is felt that it is in the patient's best interest to continue, this decision also includes the patient. • Section 14 Discontinuation from Trial Treatment was modified to delete the details on examples of intolerable drug-related toxicity since it was cumbersome and the information is included elsewhere in the protocol. • Section 19 References was modified to add the Alecensa prescribing information and update the Xalkori and Zykadia prescribing information. • Appendix B Contraceptive Guidelines was modified to indicate that women of childbearing potential should use adequate contraception for at least 45 days rather than 4 weeks (based on an update to the Xalkori prescribing information). • Appendix C Drugs That Prolong QT Interval and/or Induce Torsades De Pointes was modified/updated to Drugs with Known Risk of Torsades de Pointes based on the www.crediblemeds.org website. • Appendix E Schedule of Assessments footnote c was modified to delete "oral" and to indicate instead that it is the preferred method of assessing temperature, but other methods may be used, if necessary. • Minor clarifications and editorial changes were also made to various sections.

History of Trial Amendments

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Amendment # Amendment Date	**Revision(s) Made**
Amendment 9 29 January 2018	• The drug name 'ensartinib' has been added throughout the protocol. • Sponsor Representative was revised to Chris Liang, Ph.D. • Synopsis, Section 13.1, and Section 13.3.2 were revised to increase duration of the study to approximately 108 months and to increase enrollment to up to 190 patients with ALK genomic alterations, removing the requirement for FISH. • Synopsis and Section 2.3 were revised to add exploratory objective of exploring preliminary clinical tumor response in patients with known ALK resistance mutations. • Synopsis, Inclusion Criterion #1, and Section 7.1.5 were updated to re-open enrollment in the ALK TKI-naïve cohort and increase enrollment in this cohort to up to 25 patients. • Synopsis and Section 7.1.5 were revised to increase enrollment to up to 40 patients in the cohort for patients who have progressed on prior crizotinib and have not received other ALK TKIs. • Synopsis and Section 7.1.5 were revised to increase enrollment to up to 50 patients in the cohort for patients who have received one or more 2nd generation ALK TKI, and was revised to allow patients who have received any 2nd generation, with or without prior crizotinib. • Synopsis, Inclusion Criterion #5, Inclusion Criterion #9, and Section 7.1.5 were revised to close enrollment in the CNS and leptomeningeal disease cohorts; however, noting that patients with CNS metastases are not excluded from enrollment in other cohorts. • Synopsis, Inclusion Criterion #1, and Section 7.1.5 were revised to allow up to 20 patients with a known ALK 1198 mutation, regardless of prior therapy, to enroll. • Synopsis, Inclusion Criterion #1, and Section 7.1.5 were revised to allow enrollment in the 'Prior crizotinib and/or 2nd generation ALK TKI' cohort to have received any prior 2nd generation ALK TKI.

Amendment 9
(continued)

29 January 2018

- Synopsis, Inclusion Criterion #1, and Section 9.9.1 enrollment requirements were revised to allow enrollment using results from an FDA-approved ALK assay and remove the requirement for tissue testing. ALK TKI-naïve patients and patients with a known ALK 1198 mutation will be allowed to enroll based on local FDA-approved ALK results, and patients who have received a prior ALK TKI(s) will be allowed to enroll based on having received a prior ALK TKI, along with providing a copy of a pathology report. For ALK TKI-naïve patients, if a pathology report documenting ALK genomic alterations is not available, a fresh tumor biopsy is required and the patient may be eligible once documented ALK-positive using an FDA-approved assay.
- Synopsis and Inclusion Criterion #9 bullets with details regarding the collection of tissue were moved to become an additional bullet under Inclusion Criterion #1.
- Synopsis and Exclusion Criterion #5 were updated to specify tartrazine as a potential compound to induce an allergic reaction.
- Synopsis and Exclusion Criterion #7, and Section 7.4.1, added exclusion and prohibition of use of medications that are strong CYP3A inhibitors, strong CYP3A inducers, and CYP3A substrates with narrow therapeutic indices, with changes to subsequent numbering of the Exclusion Criteria.
- Synopsis Statistical Methodology, Section 1.2.2 and Sections 13.2.3 and 13.3 were updated with the increased enrollment numbers for each cohort, the potential improvements to the statistical evaluation and rationale for the trial.
- Synopsis Statistical Methodology was updated to clarify the use of modified RANO to evaluate CNS lesions.
- Synopsis Correlative Testing was updated to indicate that tumor tissue (with the exception of ALK TKI-naïve patients unable to provide a pathology report documenting ALK genomic alterations) (also in Section 9.9.1) and pharmacogenetics blood samples are no longer required for enrollment (also in Section 9.8).
- List of Abbreviations was updated to include next generation sequencing.
- Section 1.1 Background and Section 1.1.1.4 were revised to include updated prescribing information on alectinib and brigatinib.
- Section 1.1.1 was revised to include preliminary pre-clinical data that indicates that ensartinib has shown activity in mutants resistant to other ALK TKIs.
- Section 1.1.1.4 was updated with the most current risks associated with ensartinib.
- Section 7 was revised to all allow patients to choose whether to take ensartinib with or without food, even during Cycle 1, and indicating that ensartinib is better tolerated with food.
- Section 7.4.2 was updated to include that drugs metabolized by CYP2C9 with narrow therapeutic indices should be used with caution.
- Section 8 was revised to allow dose escalation to 250mg under certain conditions explained in detail, including the rationale for adding this option and handling of subsequent dose reduction, if required.

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TITLE: Phase I/II, First-in-Human, Dose-Escalation Study of X-396 in Patients with Advanced Solid Tumors and Expansion Phase in Patients with ALK+ Non-Small Cell Lung Cancer

Amendment # Amendment Date	**Revision(s) Made**
Amendment 9 ***(continued)*** 29 January 2018	• Section 8.2.1 was revised to allow some cases where a patient may remain on study following a Grade 3 non-hematologic toxicity lasting > 7 days or a Grade 4 non-hematologic toxicity. • Section 8.2.1 was updated to include additional types of drug-related rash reported with ensartinib. • Section 9.3 was revised to allow a reduction in the frequency of visits if after 12 months, the patient has been stable or responding to ensartinib. • Section 9.6.2 was revised to only require coagulation, testosterone, and urinalysis testing at screening/baseline. • Section 9.6.3.1 was revised to remove the requirement for triplicate ECGs to be read centrally by ERT. ECGs will still be obtained to be read at the site for safety puposes. • Section 9.6.3.2 was revised to remove the requirement to have an ophthalmology examination at screening/baseline. • Any references to assessments associated with leptomeningeal disease were removed throughout the document. • Section 9.7 was revised to only obtains sparse PK sampling moving forward. • Section 9.9.2 revised to indicate that for patients on the reduced frequency visits, biomarker samples will only be collected at cycles requiring a visit. In addition, the type of tube for collection of biomarker samples was updated. • Section 10.1 was revised to allow the pharmacy to dispense up to two cycles of study drug at a time for patients on the reduced frequency visits. • Section 11.2.3.1 was revised to provide additional detailed clarifications for evaluations of lesions and overall response. • Section 14.1 was revised to allow a patient who decides to terminate a pregnancy to remain on study, if appropriate. • Minor clarifications and editorial changes were made to various parts of the document. • Appendix B was revised to specify requirement for acceptable contraception guidelines. • Appendix C was updated with the most recent list of drugs with a known risk of Torsades de Pointes. • Appendix E was revised to accurately summarize the schedule of assessments for the edits contained in this amendment.

CLINICAL PROTOCOL X396-CLI-101 SYNOPSIS

Title of Trial:	**Phase I/II, First-in-Human, Dose-Escalation Study of X-396 in Patients with Advanced Solid Tumors and Expansion Phase in Patients with ALK+ Non-Small Cell Lung Cancer**	
Protocol Number:	X396-CLI-101	
Sponsor:	Xcovery	
Trial Duration:	The expected duration of the study is approximately 108 months.	**Phase of Trial:** I/II
Trial Centers:	This trial will enroll up to 190 patients and may include up to 50 sites, 24 of which will be in the US. Global sites may be initiated for the expansion phase of the study only.	
Objectives:	**Primary:** • To evaluate the safety/tolerability of X-396 (ensartinib) and determine the maximum tolerated dose (MTD) of X-396 (ensartinib) as a single agent. **Secondary:** • To characterize the preliminary pharmacokinetics (PK) of X-396 (ensartinib) given as a single agent. • To explore the preliminary biological activity and clinical tumor response after treatment with X-396 (ensartinib) given as a single agent. **Exploratory:** • To observe the correlation between PK and clinical endpoints. • To evaluate the status of exploratory biomarkers and correlate with clinical outcome. • To explore preliminary clinical tumor response in patients with known ALK resistance mutations. • To obtain germline DNA samples for possible pharmacogenetic analysis in the event that outliers with respect to efficacy, tolerability/safety, or exposure are identified.	
Trial Design:	A Phase I/II, first-in-human, international, multicenter, dose-escalation, open-label study of the anaplastic lymphoma kinase (ALK) and MET inhibitor X-396 (ensartinib) given as a single agent.	
Trial Population:	This study will be conducted in patients 18 years of age or older with advanced solid tumors in the dose escalation portion and with ALK+ non-small cell lung cancer (NSCLC) in the expansion cohort phase.	
Number of Patients:	Up to 190 patients are planned to be enrolled in this study.	

Trial Drug, Dose, and Mode of Administration:

X-396 (ensartinib) will be given orally on a 28 day schedule. The dosing frequency will be once daily initially, although if it is subsequently determined that it is appropriate to evaluate twice daily dosing, that will be permitted. The study will identify the MTD when X-396 (ensartinib) is administered on a daily dosing schedule. Initial dose escalation will use an accelerated titration scheme, followed by a 3 + 3 dose escalation design.

Dose Escalation (was conducted at US sites only):

Accelerated Titration Scheme: Evaluation of at least 1 patient (up to 3 patients may be enrolled at each dose level) that has completed 1 cycle (approximately 28 days) of treatment is required before escalation to the next dose level can occur. Dose escalation will progress as described in the table below. Dose escalation decisions will be made in consultation with the investigators participating in the study and the Sponsor, taking into account the safety profile of prior dose groups and available PK data.

Up to a doubling of doses will continue until 1 patient at a given dose level experiences a study drug related toxicity of ≥ Grade 2, or experiences a DLT. At this point, accelerated titration will be stopped and a standard 3 + 3 dose escalation scheme will be used for further dose escalation. In order that sufficient PK data are collected at lower doses, additional patients may be enrolled at lower doses during the accelerated titration phase.

Accelerated Titration Procedure:

Dose Level	Dose Escalation
Dose Level 1	Starting dose of 25 mg
Dose Level 2	Twice the Previous Dose
Up to a doubling of doses may continue until 1 patient experiences a study drug related toxicity of ≥ Grade 2, or experiences a DLT during the first cycle.	
Subsequent dose levels	Increase dose according to the 3 + 3 dose escalation criteria (see below)

3 + 3 Dose Escalation Scheme: Using a 3 + 3 dose escalation design, each cohort will enroll up to 6 patients. Evaluation of a cohort of at least 3 patients completing 1 cycle of treatment (approximately 28 days) is required prior to proceeding to the next dose level. Dose escalation will progress as described in the table below. Dose escalation decisions will be made in consultation with the investigators participating in the study and the Sponsor, taking into account the safety profile of prior dose groups and available PK data. Intra-patient dose escalation will be permitted as described in Section 8. At least 6 patients will be treated at the MTD level. The MTD is defined as the highest dose level in which 6 patients were treated with at most 1 patient experiencing a DLT. In order that sufficient PK data are collected at lower doses, additional patients may be enrolled at lower doses during the 3+3 dose escalation phase.

Trial Drug, Dose, and Mode of Administration: (*continued*)

"3 + 3" Dose Escalation Design:

Number of Patients with DLT	Action
0 of 3 patients	Escalate to next dose level with an increase of ≤50% [a]
1 of 3 patients	Accrue 3 additional evaluable patients at the current dose level (for a total of up to 6 evaluable patients) [b]
2 or more of 3 patients	The MTD has been exceeded. Add 3 additional patients at the previous dose level if only 3 patients had been treated at that dose level.
1 of 6 patients	Escalate to the next dose level with an increase of ≤33% [a]
2 or more patients in a dose level group of up to 6 patients	The MTD has been exceeded

[a] Where supported by available safety and PK data, dose increments will be as close to 50% or 33%, respectively, as the available dosage forms support. If it is not possible to administer a dose using the available dosage forms, the dose should be reduced to the next lowest dose supported by the available formulations (25 mg and 100 mg).

[b] For a patient to be considered "evaluable," he or she must have met the minimum safety evaluation requirements of the study, and/or experienced a DLT.

DLT:

A toxicity will be considered dose-limiting if it occurs during the first cycle (approximately 28 days) of treatment during the dose escalation phase and is determined to be possibly related to X-396 (ensartinib). DLTs will be defined as the following:

- Grade 4 neutropenia (absolute neutrophil count [ANC] <500/µL) for >5 days, or febrile neutropenia (ANC <1000/µL with fever >101ºF [38.5ºC])
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with bleeding
- Grade 3 or 4 non-hematologic toxicity (excluding Grade 3 rash, diarrhea, nausea, or vomiting if controlled with standard supportive care and lasting ≤48 hours)
- Treatment delay of ≥14 days due to unresolved toxicity

Note that isolated laboratory changes without associated signs or symptoms will be reviewed with the Medical Monitor, investigators, and Sponsor to determine whether they should be considered DLTs.

Definition of MTD:

The MTD is the highest dose at which ≤1 of 6 patients experience a DLT during 1 cycle (approximately 28 days) of therapy. If 2 or more patients in a dosing group experience a DLT, the MTD has been exceeded.

Trial Drug, Dose, and Mode of Administration (*continued*):	**Expansion Cohort Phase (potentially conducted globally):**
	225 mg once daily is the recommended Phase 2 dose (RP2D) and has been selected for the expansion cohort phase. ALK-positive cohorts will be enrolled with up to approximately 170 patients with ALK genomic alterations . The cohorts will be as follows:
	- Up to 25 patients who are ALK TKI-naïve. **As of Amendment 9, this cohort is re-opened to enrollment.**
	- Up to 40 patients who have progressed on prior crizotinib and have not received other ALK TKIs.
	- Up to 50 patients who have progressed on one or more 2nd generation ALK TKIs (patients may or may not have also received prior crizotinib). **As of Amendment 9, patients may have received any 2nd generation ALK TKI, with or without prior crizotinib.**
	- Up to 30 patients with central nervous system (CNS) metastases **(closed as of Amendment 9, though patients with CNS metastases are not excluded from enrollment in other cohorts)**. Patients in this cohort must have at least 1 CNS "target lesion" that is ≥3 mm in diameter as assessed by gadolinium-enhanced, T1-weighted brain MRI, and, if previously treated, must be at least 4 weeks post WBRT. The patients in this cohort may be ALK TKI-naïve or have progressed on prior crizotinib. To be eligible for this cohort, patients must have either:
	  - Untreated CNS metastases that are asymptomatic with respect to the CNS lesions and do not require systemic corticosteroids or anticonvulsants, or
	  - Previously treated CNS lesions that are asymptomatic. These patients may be on stable or decreasing doses of corticosteroids and anticonvulsants at least 2 weeks prior to the baseline MRI and the start of study drug. Target lesions for patients that have previously received WBRT with evidence of tumor growth at least one month post WBRT treatment as evidenced by gadolinium-enhanced MRI scan are eligible. Target lesions may not have been treated by stereotactic radiosurgery (SRS).
	- Up to 5 patients with leptomeningeal disease diagnosed by positive gadolinium uptake on MRI of the spine and/or brain with neurologic signs/symptoms, or by tumor cells in the CSF (if first CSF sample is negative for cytology, it should be repeated within 1-2 days). The patients may be ALK TKI-naïve or have progressed on prior crizotinib. **As of Amendment 9, this cohort will be closed.**
	As of Amendment 9, up to 20 patients with a known ALK 1198 mutation, regardless of prior therapy, will be allowed to enroll.

Inclusion Criteria:	1. Histologically or cytologically confirmed diagnosis of advanced solid tumor malignancy that is not responsive to at least 1 prior standard regimen for advanced disease or for which there is no approved therapy or for patients that decline standard therapy. **Note that with Amendment 9, patients that are prior ALK TKI-naïve may again agree to participate.** Patients may have received prior crizotinib and/or second generation ALK TKI(s) **(with Amendment 9, it may be any 2nd generation ALK TKI)**. • For the expanded cohort portion of the study, patients must have NSCLC with ALK genomic alterations. **Note that, with Amendment 9, the enrollment requirement for tissue testing as part of the study to demonstrate ALK genomic alterations by FISH or IHC has been removed. ALK TKI-naïve patients and patients with a known ALK 1198 mutation will be allowed to enroll based on local FDA-approved ALK results, and patients who have received a prior ALK TKI(s) will be allowed to enroll based on having received prior treatment with crizotinib and/or a 2nd generation ALK TKI. All patients will be asked to provide a copy of a pathology report demonstrating ALK genomic alterations (including the 1198 mutation for patients in that cohort).** • Patients entering this study will be asked to provide tissue for correlative testing. While collection of tissue is encouraged (fresh tumor biopsy or from a previous tissue sample), if it is not available or the patient refuses, the patient may still be eligible for enrollment. **A pathology report documenting ALK genomic alterations (including the ALK 1198 mutation for that cohort) must be sent to the Medical Monitor for review. For ALK TKI-naïve patients, if a pathology report documenting ALK genomic alterations is not available, a fresh tumor biopsy is required and the patient may be eligible once documented ALK-positive using an FDA-approved assay.** 2. Eastern Cooperative Group (ECOG) Performance Status score of 0 or 1 (see Appendix A). 3. Ability to swallow and retain oral medication. 4. Adequate organ system function, defined as follows: • Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L • Platelets $\geq 100 \times 10^9$/L • Hemoglobin ≥9 g/dL (≥90 g/L) • Total bilirubin ≤1.5 times the upper limit of normal (ULN) • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x ULN if no liver involvement or ≤5 x ULN with liver involvement. • 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, OR 24-hour measured urine creatinine clearance ≥50 mL/min. 5. Patients with treated CNS metastases are eligible if they are asymptomatic with respect to the CNS metastases and do not require escalating doses of systemic corticosteroids (i.e., stable or decreasing low-dose corticosteroids are allowed, as are stable anticonvulsants). ALK-positive patients with untreated CNS lesions may be allowed to enroll in the expansion cohort phase or previously completed dose escalation cohorts as long as the patients are asymptomatic with respect to the CNS metastases and do not require systemic corticosteroids or anticonvulsants. CNS lesions that have received SRS may not be used as target lesions.

Inclusion Criteria (*continued*):	6. Male patients willing to use adequate contraceptive measures (see Appendix B). 7. Female patients who are not of child-bearing potential, and female patients of child-bearing potential who agree to use adequate contraceptive measures and who have a negative serum or urine pregnancy test within 1 week prior to initial trial treatment (see Appendix B). 8. Patients must be ≥18 years-of-age. 9. Patients must have measurable or evaluable disease for the dose escalation portion of the study and measurable disease for the expanded cohort portion of the study. 10. Willingness and ability to comply with the trial and follow-up procedures. 11. Ability to understand the nature of this trial and give written informed consent.
Exclusion Criteria:	1. Patients currently receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy [with the exception of luteinizing hormone releasing hormone (LHRH) agonists for prostate cancer], surgery and/or tumor embolization). 2. Use of an investigational or targeted drug within 21 days or 5 half-lives (whichever is shorter) prior to the first dose of X-396 (ensartinib). A minimum of 10 days between termination of the treatment and administration of X-396 (ensartinib) is required. However, in the case of ALK TKIs, a 2-day window between termination of the TKI and the start of X-396 (ensartinib) is allowed. In addition, any drug-related toxicity should have recovered to Grade 1 or less, with the exception of alopecia. 3. Any major surgery or immunotherapy within the last 21 days (focal radiation does not require a washout period; ≥4 weeks for whole brain radiotherapy). Chemotherapy regimens with delayed toxicity within the last 4 weeks (or within the last 6 weeks for prior nitrosourea or mitomycin C). Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within the last 2 weeks. 4. Prior stem cell transplant. 5. Patients with a known allergy or delayed hypersensitivity reaction to drugs chemically related to X-396 (ensartinib) (e.g., crizotinib) or to the active ingredient of X-396 (ensartinib) or to tartrazine, a dye used in the X-396 100 mg capsules. 6. Patients with primary CNS tumors are ineligible. 7. Patients receiving: - CYP3A substrates with narrow therapeutic indices (including, but not limited to, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus) - Strong CYP3A inhibitors (including, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, grapefruit, grapefruit juice) - Strong CYP3A inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's Wort). 8. Concomitant use of herbal medications (e.g., St. John's wort, Kava, ephedra [ma huang], ginkgo biloba) at least 7 days prior to the first dose of study drug and throughout participation in the trial. 9. Females who are pregnant or breastfeeding.

Exclusion Criteria: (*continued*)	10. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of X-396 (ensartinib). 11. Clinically significant cardiovascular disease including: • QTcF interval ≥450 ms or other significant ECG abnormalities. • 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 12 months prior to Cycle 1 Day 1: • Congestive heart failure (New York Heart Class III or IV (see Appendix D)). • Cardiomyopathy. • Arrhythmia or conduction abnormality requiring medication. Note: patients with atrial fibrillation/flutter controlled by medication and arrhythmias controlled by pacemakers are eligible. • Severe/unstable angina, coronary artery/peripheral bypass graft, or myocardial infarction. • 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 known hepatitis C, or have any serious underlying medical condition that would impair the ability of the patient to receive protocol treatment. 13. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol. 14. 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. 15. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.
Statistical Methodology:	This is an open-label, Phase I/II, first-in-human, dose-escalation study of the ALK/MET inhibitor X-396 (ensartinib), with expansion cohorts at or below the MTD. This trial is designed to determine the MTD (or recommended dose based on available safety, PK, and response data) in support of dose determination for further clinical studies, and to determine the preliminary safety and PK profile and explore preliminary biological and antitumor activity of X-396 (ensartinib) given as a single agent in patients with solid tumors. Tumor response will be evaluated by the investigator. **<u>Power and Sample Size Determination:</u>** This study will enroll up to 190 patients. The number of patients treated will depend upon the need to expand the escalation cohorts from 3 to 6 based on toxicity, the total number of cohorts treated before DLT is observed and the MTD is determined, and the number of additional patients enrolled in the expansion cohort phase. Initially, this sample size was not chosen based on statistical considerations or to obtain adequate power for a particular endpoint analysis, but was chosen to allow for a preliminary safety and PK assessment of X-396 (ensartinib). As of Amendment 8, promising response rates were observed during the Phase II expansion cohort phase that were within the range of historical controls for other agents. **As of Amendment 9, to improve the precision of the estimated response rates and to gain more experience with X-396 (ensartinib) in these patient populations, the sample size for selected**

Statistical Methodology: *(continued)*	**expansion cohorts was increased, to up to 25 patients for the ALK TKI-naïve cohort, up to 40 patients for the cohort including patients that progressed on prior crizotinib and did not receive another ALK TKI, and up to 50 patients for the cohort including patients that progressed on a 2nd generation ALK TKI.** An increase to 40 patients would allow cohort response rates to be estimated within no worse than +/- 15% with 90% confidence. An increase to 50 patients would allow cohort response rates to be estimated within no worse than +/- 12% with 90% confidence. **In addition, as of Amendment 9, because of interest in the ALK 1198 resistance mutation, a cohort for patients whose tumor is known to have that mutation is being opened, with up to 20 patients allowed in that cohort.** **Statistical Methods:** Safety and PK data and antitumor activity will be examined on an ongoing basis during the study. It is anticipated that approximately 6 dose cohorts will be evaluated during the trial. The actual number of dose cohorts explored will depend upon the MTD and the safety profile observed during the conduct of the trial. Data will be listed and/or summarized and tabulated. Descriptive statistics such as mean, median, standard deviation, maximum, and minimum for continuous variables, and counts and percentages for discrete variables, will be used to summarize data. Tumors will be evaluated primarily using RECIST criteria version 1.1, although patients with CNS lesions will also be evaluated using modified RANO criteria.
Correlative Testing:	Tumor tissue (optional except for ALK TKI-naïve patients unable to provide a pathology report documenting ALK genomic alterations) and optional, but encouraged, 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 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-101 CONTACT INFORMATION:

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Safety Department (SAE Reporting):	Phone: 1-866-758-2798 Fax: 1-866-761-1274 Email: pvgsafety@novellaclinical.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
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
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood cell count
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
CMP	comprehensive metabolic profile
CNS	central nervous system
CR	complete response
CRO	contract research organization
CSF	cerebrospinal fluid
CT	computerized tomography
CTA	clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
DSMB	data safety monitoring board
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
EPHA2	Ephrin A2 kinase
ERT	eResearch Technology, Inc.
EU	European Union

List of Abbreviations (continued)

FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
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
HCl	hydrochloride salt
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HNSTD	highest non-severely toxic dose
HTN	Hypertension
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IMT	inflammatory myofibroblastic tumor
IND	Investigational New Drug
IRB	Institutional Review Board
LD	longest diameter
LTK	leukocyte tyrosine kinase
LVEF	left ventricular ejection fraction
mg	Milligram
mg/kg	milligram/kilogram
mg/m^2	milligram/meter squared
ms	Millisecond
MI	myocardial infarction
MTD	maximum tolerated dose
MUGA	multigated (radionuclide) acquisition scan
N/A	not applicable
NCI	National Cancer Institute
N/D	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
PD	progressive disease
PFS	progression-free survival
PG	pharmacogenetic
PHI	protected health information
PI	principal investigator
PK	pharmacokinetic(s)
PR+	progesterone receptor positive
QA	quality assurance
QD	once daily
QTc	QT interval corrected for heart rate
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors
RET	RET oncogene "Rearranged during transfection"
ROS1	transforming gene of avian sarcoma virus UR2
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinases
SAR	suspected adverse reaction
SAE	serious adverse event
SCRI	Sarah Cannon Research Institute
SD	stable disease
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
TKI	tyrosine kinase inhibitor
TTP	time to tumor progression
UK	United Kingdom
ULN	upper limit of normal
US	United States
WBRT	whole brain radiation therapy

Table of Contents

List of Tables

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 et al. 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 have entered into clinical trials. The first agent in humans was crizotinib (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. 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 fusion-positive NSCLC demonstrated a >60% radiographic response rate (Bang et al. 2008). By contrast, chemotherapy response rates are <10% in previously treated patients with unselected NSCLC (Hanna et al. 2004). Since crizotinib was approved for marketing, several 2nd generation ALK TKIs (ceritinib, alectinib, and brigatinib) have also been approved in the U.S.

1.1.1. X-396 (Ensartinib)

Xcovery Holdings, Inc. (the Sponsor) has developed X-396 (ensartinib), a novel potent and specific ALK inhibitor with potential therapeutic relevance. In *in vitro* and *in vivo* nonclinical studies, X-396 (ensartinib) exhibited a favorable effectiveness profile, including anti-tumor activity against multiple ALK variants including those that are resistant or become resistant to crizotinib and alectinib. In particular, ensartinib potently inhibits the I1171N/T mutants that are resistant to alectinib. It is more potent against the L1198F mutant than all known ALK inhibitors in clinical development (crizotinib, alectinib, ceritinib, brigatinib, and lorlatinib) (Lovly, private communication).

1.1.1.1. Toxicology

To assess the safety of X-396 (ensartinib), toxicity studies were conducted in rats and dogs, including pivotal 28-day toxicity studies. In these studies, X-396 (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 X-396 (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 (STD10).

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.

There was no indication that X-396 (ensartinib) adversely affected the core organ systems (i.e., cardiovascular, respiratory, central nervous systems) in the repeat-dose toxicology 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 X-396 (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.

X-396 (ensartinib) exhibited tumor levels in mice that were 2 to 6 times plasma concentrations at 2 or 4 hr. Brain concentrations were approximately 5 to 15% of plasma concentrations at the same time, indicating preferential distribution to the tumor relative to plasma or brain.

X-396 (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.

X-396 (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 the concentrations anticipated to be achieved in the clinic (<2 μM), this would not suggest the potential for drug-drug interactions.

Refer to the X-396 (ensartinib) IB for detailed information regarding the PK studies conducted to date.

1.1.1.3. Pharmacology/Pharmacodynamic Studies

X-396 (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 X-396 (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, C1156Y) that confer resistance to crizotinib in the clinic were potently inhibited by X-396 (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 (ensartinib) may be effective in mutant cells resistant to crizotinib (Lovly et al. 2011).

X-396 (ensartinib) was 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 (ensartinib) (Yap et al. 2010; Tandon et al. 2011).

In animal studies, X-396 (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 by X-396 (ensartinib). These same cells were adapted to an intracranial model and treated with X-396 (ensartinib) and crizotinib at equivalent doses. A significant increase in life span was observed in mice treated with X-396 (ensartinib) but not in mice treated with crizotinib in this brain penetration model. These data support the potential utility of X-396 (ensartinib) in

crizotinib-resistant tumors and support the potential use of X-396 (ensartinib) for the treatment of NSCLC tumors that have metastasized to the brain.

Refer to the X-396 (ensartinib) IB for detailed information regarding the pharmacodynamic (PD) studies conducted to date.

1.1.1.4. X-396 (ensartinib) Overall Risk Assessment

The current risk profile for X-396 (ensartinib) is based on safety data collected from completed nonclinical studies and from ongoing trials with X-396, as well as from labeling for similar products, crizotinib (Xalkori®), ceritinib (Zykadia®), alectinib (Alecensa®), and brigatinib (Alunbrig®).

Nonclinical data on X-396 (ensartinib): From the X-396 (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 X-396 (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 accompanied by reduced food consumption (male dogs excepted). Histopathology findings included skin changes (e.g., acanthosis/hyperkeratosis, inflammation, squamous cell hyperplasia, and ulcers), stomach changes in rat (hyperkeratosis), and hypocellularity of the bone marrow and lymphoid depletion of the spleen and thymus in dog. Clinical pathology findings were generally mild to moderate, and many of the findings, particularly in the dog, were observed only at the highest dose studied. Clinical pathology 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.

Clinical data on X-396 (ensartinib): To date, the most common drug-related AEs (≥10% of patients) observed with X-396 (ensartinib) from the Phase I/II study include rash (including rash, erythema, erythematous rash, follicular rash, macular rash, maculopapular rash, acneiform rash, pruritic rash, skin exfoliation, pustular rash, eczema, lichenoid keratosis/dermatitis, and photosensitivity), nausea, pruritus, vomiting, fatigue, edema (including peripheral edema, facial edema, periorbital edema), decreased appetite, dry skin, diarrhea, AST increased, ALT 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.
- Grade 3 dyspnea that resolved while continuing on study drug. It is not clear whether it was related to study drug or to the patient's underlying disease. The evaluation is ongoing and the SAE report has not been finalized at this time.

Patients described above experiencing thrombotic microangiopathy, elevated ALT and bilirubin, pneumonitis, and the dehydration with UTI were discontinued from the study; the patient experiencing dyspnea is undergoing evaluation and it is unclear whether they are going to remain on study; all others were able to tolerate a regimen where the dose was held and/or continued or reduced.

Separately, under and Investigator IND, 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.

Clinical data from products of the same class: 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, pancreatitis/pancreatic enzyme elevation, renal impairment, severe visual loss/visual disturbance, 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, vitreous detachment, reduced visual acuity, macular edema, visual field defects, asthenopia), nausea, vomiting, diarrhea, constipation, esophageal disorder (including dyspepsia, gastroesophageal reflux, dysphagia), abdominal pain, bradycardia, prolonged QT interval, hypertension, edema, fatigue, upper respiratory infection, pneumonia, fever, cough, dyspnea, elevated transaminases, decreased appetite, weight decreased, weight increased, myalgia, muscle spasms, musculoskeletal pain, non-cardiac chest pain, pain in extremity, back pain, arthralgia, dizziness/balance disorder, headache, insomnia, neuropathy, dysgeusia, renal impairment, 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 X-396 (ensartinib) will be observed in the clinical trials is unknown.

1.2. Rationale

1.2.1. Rationale for Selection of the Starting Dose

The initial dose in clinical trials has been calculated according to the guidance given in Note 2 of ICH S9, which states the following: "A common approach for many small molecules is to set a start dose at 1/10 the severely toxic dose in 10% of the animals (STD_{10}) in rodents. If the non-rodent is the most appropriate species, then 1/6 the highest non-severely toxic dose (HNSTD) is considered an appropriate starting dose. The HNSTD is defined as the highest dose level that does not produce evidence of lethality, life-threatening toxicities or irreversible findings."

For X-396 (ensartinib), the STD_{10} in rodents is considered to be 50 mg/kg/day, and the HNSTD in dogs is considered to be 15 mg/kg/day. Using allometric scaling, this gives the following calculations:

- For the rat, 50 mg/kg/day is equivalent to 300 mg/m^2. 1/10 of this is 30 mg/m^2, equivalent to approximately 50 mg to a 1.62 m^2 human (FDA Guidance 2005).
- For the dog, 15 mg/kg/day is equivalent to 300 mg/m^2. 1/6 of this is approximately 50 mg/m^2, equivalent to approximately 80 mg to a 1.62 m^2 human (FDA Guidance 2005).

Taking the most sensitive species as the guide (the rat, in this case), toxicology data suggests an initial dose of 50 mg for the Phase 1, first in human clinical (FIH) trial. However, subsequent to the initiation of the good laboratory practice (GLP) toxicology studies, it was determined that X-396 (ensartinib) is a dihydrochloride salt rather than a monohydrochloride salt. Additionally, the moisture content of X-396 (ensartinib) is <7%. To account for the adjustments due to additional HCl and moisture, the Sponsor has decided that the clinical starting dose will be 25 mg (based on the free base).

1.2.2. Rationale for the Trial

This study will determine the maximum tolerated dose (MTD) and preliminary PK characteristics of X-396 (ensartinib), as well as preliminary information on the antitumor activity, when administered as a single agent. **As of Amendment 9, good antitumor activity has been observed in this trial in ALK TKI-naïve patients, patients that received prior crizotinib, and patients with CNS metastases. In addition, responses have been observed in patients that received prior 2nd generation ALK TKIs. As new ALK TKIs become more widely used, it is of interest to obtain additional experience with X-396 (ensartinib) in patients that are ALK TKI-naïve and patients that progressed on other ALK TKI(s). As a result, the cohorts for ALK TKI-naïve patients and patients that received prior crizotinib and prior 2nd generation ALK TKIs are being expanded with this amendment. In addition, in vitro data from Christine Lovly's lab indicated that X-396 (ensartinib) potently inhibits the I1171N/T mutants that are resistant to alectinib and the L1198F mutant that is resistant to lorlatinib, alectinib, brigatinib, and ceritinib. There is interest in the sensitivity and resistance of the 1198 mutation to different ALK TKIs. To explore this with X-396 (ensartinib), patients with known 1198 mutations may be enrolled in a separate cohort.**

This trial will be conducted in accordance with the International Conference on Harmonisation (ICH) guideline on Good Clinical Practice (GCP) (E6) [ICH/GCP], US 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 safety/tolerability of X-396 (ensartinib) and determine the MTD of X-396 (ensartinib) administered as a single agent.

2.2. Secondary Objectives

The secondary objectives of this trial are:

- To characterize the preliminary pharmacokinetics (PK) of X-396 (ensartinib) administered as a single agent.
- To explore the preliminary biological activity and clinical tumor response after treatment with X-396 (ensartinib) administered as a single agent.

2.3. Exploratory Objectives

- To observe the correlation between PK and clinical endpoints.
- To evaluate the status of exploratory biomarkers and correlate with clinical outcome.
- To explore preliminary clinical tumor response in patients with known ALK resistence mutations.

- 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 Endpoints

- Dose-limiting toxicities (DLTs) and other adverse events to determine the MTD

3.2. Secondary Endpoints

- PK data
- Pharmacodynamic (PD) and possible pharmacogenetic (PG) assessments
- Objective tumor response as assessed by the investigator

4. TRIAL DESIGN

This study is a Phase I/II, first in human (FIH) dose-escalation, international, multicenter, open-label study of the ALK/MET inhibitor X-396 (ensartinib) given as a single agent. This trial will enroll up to 190 patients and may include up to 50 sites, 24 of which will be in the US. Global sites may be initiated for the expansion phase of the study only.

In this study, X-396 (ensartinib) will be given orally daily on a 28-day schedule. The study will identify an MTD (see Section 7.1.4) when X-396 (ensartinib) is administered on a continuous dosing schedule.

Initial dose escalation will use an accelerated titration scheme (see Section 7.1.1), followed by a 3 + 3 dose escalation design (see Section 7.1.2). The dosing frequency will be once daily initially, although twice daily dosing may be evaluated if it is subsequently determined that it is appropriate to do so. In order that sufficient PK data are collected at doses below the MTD, additional patients may be enrolled at lower doses during the accelerated titration and/or 3+3 dose escalation phases.

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 solid tumor malignancy that is not responsive to at least 1 prior standard regimen for advanced disease or for which there is no approved therapy or for patients that decline standard therapy. **Note that with Amendment 9, patients that are prior ALK TKI-naïve may again agree to participate.** Patients may have received prior crizotinib and/or second generation ALK TKI(s) **(with Amendment 9, it may be any 2nd generation ALK TKI)**.

- For the expanded cohort portion of the study, patients must have NSCLC with ALK genomic alterations. **Note that, with Amendment 9, the enrollment requirement for tissue testing as part of the study to demonstrate ALK genomic alterations by FISH or IHC has been removed. ALK TKI-naïve patients and patients with a known ALK 1198 mutation will be allowed to enroll based on local FDA-approved ALK results and patients who have received a prior ALK TKI(s) will be allowed to enroll based on having received prior treatment with crizotinib and/or a 2nd generation ALK TKI. All patients will be asked to provide a copy of a pathology report demonstrating ALK genomic alterations (including the 1198 mutation for patients in that cohort).**
- Patients entering this study will be asked to provide tissue for correlative testing. While collection of tissue is encouraged (fresh tumor biopsy or from a previous tissue sample), if it is not available or the patient refuses, the patient may still be eligible for enrollment. **A pathology report documenting ALK genomic alterations (including the ALK 1198 mutation for that cohort) must be sent to the Medical Monitor for review. For ALK TKI-naïve patients, if a pathology report documenting ALK genomic alterations is not available, a fresh tumor biopsy is required and the patient may be eligible once documented ALK-positive using an FDA-approved assay.**

2. Eastern Cooperative Group (ECOG) Performance Status score of 0 or 1 (see Appendix A).
3. Ability to swallow and retain oral medication.
4. Adequate organ system function, defined as follows:
   - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
   - Platelets $\geq 100 \times 10^9$/L
   - Hemoglobin ≥9 g/dL (≥90 g/L)
   - Total bilirubin ≤1.5 times the upper limit of normal (ULN)
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3x ULN if no liver involvement or ≤5 x ULN with liver involvement.
   - Creatinine ≤ 1.5x ULN. If >1.5x ULN, patient may still be eligible if calculated creatinine clearance ≥50 mL/min (0.83 mL/s) as calculated by the Cockcroft-Gault method, OR 24-hour measured urine creatinine clearance ≥50 mL/min.
5. Patients with <u>treated CNS metastases</u> are eligible if they are asymptomatic with respect to the CNS metastases and do not require escalating doses of systemic corticosteroids (i.e., stable or decreasing low-dose corticosteroids are allowed, as are stable anticonvulsants). ALK-positive patients with <u>untreated CNS lesions</u> may be allowed to enroll in the expansion cohort phase or previously completed dose escalation cohorts as long as the patients are asymptomatic with respect to the CNS metastases and do not require systemic corticosteroids or anticonvulsants. CNS lesions that have received SRS may not be used as target lesions.

6. Male patients willing to use adequate contraceptive measures (see Appendix B).
7. Female patients who are not of child-bearing potential, and female patients of child-bearing potential who agree to use adequate contraceptive measures and who have a negative serum or urine pregnancy test within 1 week prior to initial trial treatment (see Appendix B).
8. Patients must be ≥18 years-of-age.
9. Patients must have measurable or evaluable disease for the dose escalation portions of the study and measurable disease for the expanded cohort portion of the study.
10. Willingness and ability to comply with the trial and follow-up procedures.
11. Ability to understand the nature of this trial and give written informed consent.

5.2. Exclusion Criteria

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

1. Patients currently receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy [with the exception of luteinizing hormone releasing hormone (LHRH) agonists for prostate cancer], surgery and/or tumor embolization).
2. Use of an investigational or targeted drug within 21 days or 5 half-lives (whichever is shorter) prior to the first dose of X-396 (ensartinib). A minimum of 10 days between termination of the treatment and administration of X-396 (ensartinib) is required. However, in the case of ALK TKIs, a 2-day window between termination of the TKI and the start of X-396 (ensartinib) is allowed. In addition, any drug-related toxicity should have recovered to Grade 1 or less, with the exception of alopecia.
3. Any major surgery or immunotherapy within the last 21 days (focal radiation does not require a washout period; ≥4 weeks for whole brain radiotherapy). Chemotherapy regimens with delayed toxicity within the last 4 weeks (or within the last 6 weeks for prior nitrosourea or mitomycin C). Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within the last 2 weeks.
4. Prior stem cell transplant.
5. Patients with a known allergy or delayed hypersensitivity reaction to drugs chemically related to X-396 (ensartinib) (e.g., crizotinib) or to the active ingredient of X-396 (ensartinib), or to tartrazine, a dye used in the X-396 (ensartinib) 100 mg capsules.
6. Patients with primary CNS tumors are ineligible.
7. Patients receiving:
   - CYP3A substrates with narrow therapeutic indices (including, but not limited to, alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus)
   - Strong CYP3A inhibitors (including, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir,

telithromycin, troleandomycin, voriconazole, grapefruit, grapefruit juice)
- Strong CYP3A inducers (including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's Wort).

8. Concomitant use of herbal medications (e.g., St. John's wort, Kava, ephedra [ma huang], ginkgo biloba) at least 7 days prior to the first dose of study drug and throughout participation in the trial.
9. Females who are pregnant or breastfeeding.
10. Presence of active gastrointestinal (GI) disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of X-396 (ensartinib).
11. Clinically significant cardiovascular disease including:
    - QTcF interval ≥450 ms or other significant ECG abnormalities.
    - 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 12 months prior to Cycle 1 Day 1:
    - Congestive heart failure (New York Heart Class III or IV (see Appendix D).
    - Cardiomyopathy.
    - Arrhythmia or conduction abnormality requiring medication. Note: patients with atrial fibrillation/flutter controlled by medication and arrhythmias controlled by pacemakers are eligible.
    - Severe/unstable angina, coronary artery/peripheral bypass graft, or myocardial infarction.
    - 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 known hepatitis C, or have any serious underlying medical condition that would impair the ability of the patient to receive protocol treatment.
13. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
14. 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.
15. Inability or unwillingness to comply with study and/or follow-up procedures outlined in the protocol.

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)/ Ethics Committee (EC) approval of this protocol and consent form are required.

7. ADMINISTRATION OF X-396 (ENSARTINIB)

All patients entering this study will initially receive X-396 (ensartinib) PO once daily, although if it is subsequently determined that it is appropriate to evaluate twice daily dosing, that will be permitted (with doses taken approximately 12 hours apart). For the dose escalation portion of the study, patients will be instructed to take medication either 1 hour (or more) before mealtime or 2 hours (or more) after mealtime. X-396 (ensartinib) should be administered in a fasting state, unless permission is given by the Medical Monitor for the patient to receive the study medication with food (see below).

The decision may be made to explore dosing under fed conditions. If this occurs, the starting dose would occur at a dose below the MTD under fasted conditions and patients would be instructed to take the study drug within 30 minutes after a meal.

For the expansion cohort phase, approximately half of the patients will be instructed to take the study medication with food (within 30 minutes after a meal) and half will be instructed to take the study medication under fasting conditions (1 hour or more before mealtime or 2 hours or more after mealtime) in Cycle 1. At the time of patient enrollment, the sites will be instructed whether the patient is to take the study drug with or without food. After Cycle 1, patients may choose to take the study drug with or without food; however, the time of day for administration of X-396 (ensartinib) should be consistent. **Note: with Amendment 9, patients may take study medication with or without food (even during Cycle 1), although it should be noted that X-396 (ensartinib) is better tolerated with food.** 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 will be instructed to take the dose as soon as possible, but not less than 12 hours before the next dose is due for once daily dosing and not less than 6 hours before the next dose is due for twice daily dosing. If the next dose is due in less than 12 hours or 6 hours for once daily and twice daily dosing, respectively, the patient will be instructed to skip the missed dose and take the next dose as scheduled.

If vomiting occurs after taking the study medication, the patient will be instructed not to retake the dose and they will be instructed to take the next scheduled dose of X-396 (ensartinib). If vomiting persists, the patient will be instructed to contact the investigator. The investigator may discuss this with the Medical Monitor and, if unable to control the vomiting with anti-emetics, the Medical Monitor may deem it appropriate for the patient to take the study medication with food if they had been taking the study drug under fasting conditions.

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.

7.1. Dose Escalation Procedure (was conducted at US sites only)

It is anticipated that approximately 6 dose cohorts will be evaluated during the trial. The actual number of dose cohorts explored will depend upon the MTD and the safety profile observed during the conduct of the trial. Up to a doubling of doses may continue until 1 patient experiences a possible study drug-related toxicity of ≥ Grade 2, or experiences a DLT during the first cycle. See Table 1 and Table 2 for details. In order that sufficient PK data are collected at

doses below the MTD, additional patients may be enrolled at lower doses during the accelerated titration and/or 3+3 dose escalation phase.

7.1.1. Accelerated Titration Scheme

Evaluation of at least 1 patient (up to 3 patients may be enrolled at each dose level) that has completed 1 cycle (approximately 28 days) of treatment is required before escalation to the next dose level can occur. Dose escalation will progress as described in Table 1. Dose escalation decisions will be made in consultation with the investigators participating in the study and the Sponsor, taking into account the safety profile of prior dose groups and available PK data. Intra-patient dose escalation is not permitted. Up to a doubling of doses will continue until 1 patient at a given dose level experiences a study drug related toxicity of ≥ Grade 2, or experiences a DLT (see Section 7.1.3). At this point, accelerated titration will be stopped and a standard 3 + 3 dose escalation scheme will be used for further dose escalation. In order that sufficient PK data are collected at lower doses, additional patients may be enrolled at lower doses during the accelerated titration phase.

Table 1 Accelerated Titration Procedure

Dose Level	Dose Escalation
Dose Level 1	Starting dose of 25 mg
Dose Level 2	Twice the previous dose
Up to a doubling of doses may continue until 1 patient at a given dose level experiences study drug-related toxicity of ≥ Grade 2, or a DLT during the first cycle.	
Subsequent dose levels	Increase dose according to the 3 + 3 dose escalation criteria (see Table 2)

7.1.2. The 3 + 3 Dose Escalation Design

Using a 3 + 3 dose escalation design, each cohort will enroll up to 6 patients. Evaluation of a cohort of at least 3 patients completing 1 cycle of treatment (approximately 28 days) is required prior to proceeding to the next dose level. Dose escalation will progress as described in Table 2. Dose escalation decisions will be made in consultation with the investigators participating in the study and the Sponsor, taking into account the safety profile of prior dose groups and available PK data. Intra-patient dose escalation will be permitted as described in Section 8. At least 6 patients will be treated at the MTD level. The MTD is defined as the highest dose level at which 6 patients were treated with at most 1 patient experiencing a DLT. In order that sufficient PK data are collected at lower doses, additional patients may be enrolled at lower doses during the 3+3 dose escalation phase.

Table 2 Dose Escalation (3 + 3) Design

Number of Patients with DLT	Action
0 of 3 patients	Escalate to next dose level with an increase of ≤50% [a]
1 of 3 patients	Accrue 3 additional evaluable patients at the current dose level (for a total of up to 6 evaluable patients) [b]
2 or more of 3 patients	The MTD has been exceeded. Add 3 additional patients at the previous dose level if only 3 patients had been treated at that dose level.
1 of 6 patients	Escalate to the next dose level with an increase of ≤33% [a]
2 or more patients in a dose level group of up to 6 patients	The MTD has been exceeded

[a] Where supported by available safety and PK data, dose increments will be as close to 50% or 33%, respectively, as the available dosage forms support. If it is not possible to administer a dose using the available dosage forms, the dose should be reduced to the next lowest dose supported by the available formulations (25 mg and 100 mg).

[b] For a patient to be considered "evaluable," he or she must have met the minimum safety evaluation requirements of the study, and/or experienced a DLT.

7.1.3. Dose-Limiting Toxicity

A toxicity will be considered dose-limiting if it occurs during the first cycle (approximately 28 days) of treatment with X-396 (ensartinib) during the dose escalation phase and is determined to be possibly related to X-396 (ensartinib). Dose-limiting toxicities will be defined as the following:

- Grade 4 neutropenia (ANC <500/μL [<0.5 x 10^9/L]) for >5 days, or febrile neutropenia (ANC <1000/μL [<1.0 x 10^9/L] with fever >101ºF [38.5ºC])
- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with bleeding
- 3 or 4 non-hematologic toxicity (excluding Grade 3 rash, diarrhea, nausea, or vomiting if controlled with standard supportive care and lasting ≤48 hours
- Treatment delay of ≥14 days due to unresolved toxicity

Note that isolated laboratory changes without associated signs or symptoms will be reviewed with the Medical Monitor, investigators, and Sponsor to determine whether they should be considered DLTs.

7.1.3.1. Determination of DLT

The patient population used for determination of DLT will consist of patients who have met the minimum safety evaluation requirements of the study and/or who have experienced a DLT. Minimum safety requirements will be met if, during Cycle 1 of treatment, the patient receives at least 80% of planned total doses of X-396 (ensartinib), completes the required safety evaluations, and is observed for at least 28 days following the first dose of X-396 (ensartinib).

Patients who discontinue treatment early due to disease progression or withdrawal will be asked to have all end-of-treatment safety evaluations performed as described in the protocol (see Appendix E). If a patient withdraws from treatment during Cycle 1 due to any reason other than

DLT and does not meet the minimum requirements for inclusion in the MTD-determining population described above, that patient will be replaced if needed to have enough patients evaluated for a decision on dose escalation.

7.1.4. Maximum Tolerated Dose

The MTD is the highest dose at which ≤1 of 6 patients experience a DLT during the first cycle (approximately 28 days) of therapy. If 2 or more patients in a dosing group experience a DLT, the MTD has been exceeded.

7.1.5. Expansion Cohort Phase (potentially conducted globally)

225 mg once daily is the recommended Phase 2 dose (RP2D) and has been selected for the expansion cohort phase. ALK-positive cohorts will be enrolled with up to approximately 170 NSCLC patients with ALK genomic alterations. The cohorts will be as follows:

- Up to 25 patients who are ALK TKI-naïve. **As of Amendment 9, this cohort is re-opened to enrollment.**
- Up to 40 patients who have progressed on prior crizotinib and have not received other ALK TKIs.
- Up to 50 patients who have progressed on one or more 2nd generation ALK TKIs (patients may or may not have also received prior crizotinib). **As of Amendment 9, patients may have received any 2nd generation ALK TKI, with or without prior crizotinib.**
- Up to 30 patients with central nervous system (CNS) metastases **(closed as of Amendment 9, though patients with CNS metastases are not excluded from enrollment in other cohorts)**. Patients in this cohort must have at least 1 CNS "target lesion" that is ≥3 mm in diameter as assessed by gadolinium-enhanced, T1-weighted brain MRI, and, if previously treated, must be at least 4 weeks post WBRT. The patients in this cohort may be ALK TKI-naïve or have progressed on prior crizotinib. To be eligible for this cohort, patients must have either:
    - Untreated CNS metastases that are asymptomatic with respect to the CNS lesions and do not require systemic corticosteroids or anticonvulsants, or
    - Previously treated CNS lesions that are asymptomatic. These patients may be on stable or decreasing doses of corticosteroids and anticonvulsants at least 2 weeks prior to the baseline MRI and the start of study drug. Target lesions for patients that have previously received WBRT with evidence of tumor growth at least one month post WBRT treatment as evidenced by gadolinium-enhanced MRI scan are eligible. Target lesions may not have been treated by stereotactic radiosurgery (SRS).
- Up to 5 patients with leptomeningeal disease diagnosed by positive gadolinium uptake on MRI of the spine and/or brain with neurologic signs/symptoms, or by tumor cells in the CSF (if first CSF sample is negative for cytology, it should be repeated within 1-2 days).

The patients may be ALK TKI-naïve or have progressed on prior crizotinib. **As of Amendment 9, this cohort will be closed.**

- **As of Amendment 9, up to 20 patients with a known ALK 1198 mutation, regardless of prior therapy, will be allowed to enroll.**

The additional patients in the expanded cohort phase will help to further characterize the safety and PK profile and evaluate preliminary antitumor activity of X-396 (ensartinib). In addition, these patients will help to define the recommended X-396 (ensartinib) dose to be used in further clinical studies. If deemed appropriate, the expanded cohort may include patients from the dose escalation portion of the study treated at the dose chosen for the expansion cohort phase. If appropriate, additional expansion of cohorts (up to 10 patients) in ALK-positive patients at lower doses may also be undertaken to better characterize the safety profile and thereby define the recommended Phase 2 dose.

7.2. Supportive Care

Patients should receive appropriate supportive care for underlying medical conditions/adverse events, at the discretion of the investigator. If such treatments are prohibited by the protocol, this should be discussed with the Medical Monitor and the patient should be removed from the trial unless allowed to continue by the Medical Monitor.

Use of erythropoietin replacement or bisphosphonates is considered supportive care, and their use **is** permitted, at the investigator's discretion, if initiated >2 weeks prior to trial treatment or initiated after Cycle 1.

Prophylactic granulocyte colony-stimulating factor (G-CSF) is **prohibited**. However, at the discretion of the treating physician, patients may receive therapeutic G-CSF after Cycle 1 if neutropenia occurs. Therapeutic use of G-CSF should follow standard American Society of Clinical Oncology (ASCO) guidelines.

Transfusions may be given, based on standard criteria and clinical judgment.

Patients are permitted to receive palliative radiation therapy on study after Cycle 1 at the discretion of the treating physician for existing bone metastases if there is no evidence of progressive disease elsewhere. Radiation therapy after Cycle 1 for isolated CNS metastases may be permitted 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.

7.3. 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 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.

7.4. 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.

7.4.1. Prohibited Concomitant Medications

The following treatments are prohibited while on the clinical trial: any cancer treatment other than the study medication, including radiation therapy (except for palliative radiation therapy, as noted under Supportive Care), chemotherapy, hormonal therapy for cancer (with the exception of LHRH agonists for prostate 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).
- Drugs that are strong CYP3A inducers (including but not limited to carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort).
- Herbal preparations and medications are not permitted throughout the trial. Examples include: St. John’s wort, Kava, ephedra (ma huang), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications at least 7 days prior to the first dose of study drug.

7.4.2. Concomitant Medications to Be Used with Caution

- As ensartinib inhibits CYP2C9, drugs metabolized by CYP2C9 with narrow therapeutic indices (including, but not limited to phenytoin and warfarin) should be used with caution.
- Concomitant treatment with medications with a known risk for Torsades de Pointes should be used with caution (see Appendix C).

8. DOSE MODIFICATIONS

With Amendment 4, intra-patient dose escalation will be permitted in the dose escalation phase after at least 2 cycles, based on the judgment of the investigator as long as the patient meets the following criteria:

- the patient does not have disease progression per RECIST assessment
- the patient has not experienced ≥ Grade 1 related toxicity or required a dose reduction or interruption due to drug-related toxicity (see below).

The dose may be escalated by 1 dose level, as long as that level has been determined not to exceed the MTD. A second dose escalation may occur after at least 2 additional cycles at the escalated dose and the patient continues to meet the conditions above.

In the expansion phase, if the dose had previously been reduced, dose escalation back to a previously given dose level may take place if the 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) or it is otherwise thought to be appropriate to try escalating back to the prior dose. However, this must be discussed with, and agreed to, by the Medical Monitor.

In addition, with Amendment 9, optional dose escalation to 250 mg may occur under certain conditions. If no grade 2 or greater rash is observed after at least one cycle on X-396 (ensartinib), and there are no AEs of concern, the PI will have the discretion to escalate the dose to 250 mg. This is being permitted since the MTD was not officially reached during the dose escalation portion of the study. At that time, the severity of rash was higher (Grade 3) at 250 mg than had been seen at lower doses, including what had been observed initially at 225 mg. As a result, 225 mg was chosen as the recommended Phase II dose. As more patients were treated with 225 mg, Grade 3 rashes were also observed at that dose level. However, as experience was gained, it was found that the rash is generally easily managed. In addition, there have been a number of patients who experienced responses but subsequently progressed in the CNS while continuing to do well systemically. Since the 250 mg dose was evaluated in the dose escalation portion and was not determined to exceed the MTD, this higher dose will be explored further in order to give these patients the best chance of responding and maintaining the response.

Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. 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. Treatment with X-396 (ensartinib) will be held in any patient experiencing a DLT as described in Section 7.1.3 at any time during the study. Dose modifications following a DLT will be according to the dose modifications below. For the expansion cohort phase, the starting dose is 225 mg qd. If dose reductions are necessary, as noted in this section, the dose levels will be 225 mg qd for any patient that was escalated to 250 mg, 200 mg qd, and then, if necessary, 150 mg qd (see Table 3).

Table 3 Dose Levels for Expansion Cohort Phase

Dose Level +1**	250 mg qd
Starting Dose	225 mg qd
Dose Level -1*	200 mg qd
Dose level -2*	150 mg qd

* If dose reductions are necessary
**** With Amendment 9, see text above for circumstances when this may be done**

As noted, 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 Modifications Due to Drug-Related Hematologic Toxicity

If hematologic toxicity occurs, treatment with X-396 (ensartinib) should be held (see Table 4) and re-evaluated 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 4. If ANC and/or platelets do not recover within 4 weeks the patient should be permanently discontinued from trial treatment.

Table 4 Dose Modifications Due to Drug-Related Hematologic Toxicities

Event	X-396 (ensartinib) Dose [c]
Neutropenia (ANC)	
ANC <0.5 x 10^9/L (Grade 4)	Hold dose [a] until recovery to ≤ Grade 2 [ANC ≥1.0 x 10^9/L], then resume X-396 (ensartinib) at one lower dose level [b].
Recurrence of ANC <0.5 x 10^9/L (Grade 4)	Hold dose [a] until ANC recovery to ≤ Grade 2 [ANC ≥1.0 x 10^9/L], then resume X-396 (ensartinib) at one lower dose level [b].
Thrombocytopenia	
Platelets <50 x 10^9/L (Grade 3)	Hold dose [a] until improvement to Platelets ≥75 x 10^9/L • If resolved in ≤5 days, then resume without a dose reduction [b]. • If resolved in >5 days but <4 weeks, then resume dose at one lower dose level [b].

[a] Hold X-396 (ensartinib) treatment; do at least weekly CBC with differential until toxicity resolves (ANC recovery ≥1.0 x 10^9/L and Platelets ≥75 x 10^9/L).

[b] Re-treatment criteria = ANC recovery ≥1.0 x 10^9/L and Platelets ≥75 x 10^9/L. For dose levels for expansion cohort phase, see Table 3.

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

8.2. Dose Modifications Due to Drug-Related Non-Hematologic Toxicities

8.2.1. Grade 3 or 4 Non-Hematologic Toxicity

The dose reduction guidelines for drug-related non-hematologic toxicities are shown in Table 5. If a Grade 3 non-hematologic toxicity that is expected to be manageable and reversible with dose reduction occurs, treatment with X-396 (ensartinib) 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, except as noted below. Patients with Grade 3 non-hematologic toxicity lasting ≤7 days that does not resolve to baseline or ≤ Grade 1 within 4 weeks should also be removed from the trial treatment. If a Grade 4 non-hematologic toxicity occurs, study drug will 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.

Specific Recommendations for Drug-Related Rash:

To date, the most common drug-related adverse event with X-396 (ensartinib) been rash, primarily Grade 1-2. Although different types of rash have been reported for X-396 (ensartinib) (rash, erythematous rash, macular rash, maculopapular rash, pruritic rash, acneiform dermatitis, follicular rash, pustular rash, erythema, skin exfoliation, eczema, lichenoid keratosis/dermatitis, and photosensitivity), the predominant type of rash seems to be the erythematous rash, described sometimes as a sunburn-type rash (generally, however, it does not appear to be phototoxicity). Some of these have been Grade 3, generally with pruritus and sometimes with peeling. It has begun as early as Cycle 1 Day 4 and in other cases not until Cycle 2, rarely beginning beyond Cycle 2.

Based on the experience with X-396 (ensartinib) to date, the recommendations for treating rashes considered related to X-396 (ensartinib) are as follows. For Grade 3 rash, hold X-396 (ensartinib) until resolution to ≤ Grade 1, then resume treatment at a reduced dose. For Grade 1-2 rashes, topical corticosteroids may be used, if appropriate. If it is felt that short-term courses of oral corticosteroids are needed, it is suggested that the dose of X-396 (ensartinib) be held until improvement to ≤ Grade 1, then resume X-396 (ensartinib) at a reduced dose. Of course, the investigator should treat the patient as he/she feels is most appropriate, including the use of allowed concomitant medications and holding and/or reducing the dose of X-396 (ensartinib). If appropriate, a skin biopsy and pictures of the rash are encouraged to try to obtain a better understanding of these rashes (see Section 9.9.3).

Specific Recommendations for Drug-Related Nausea, Vomiting and Diarrhea:

For patients with Grade 3 nausea, vomiting, and/or diarrhea considered related to X-396 (ensartinib), X-396 (ensartinib) should be held and supportive care initiated. If the Grade 3 toxicity lasts ≤7 days, patients may restart X-396 (ensartinib) at a reduced dose when toxicity returns to ≤ Grade 1. If the patient has recurrent Grade 3 toxicity despite supportive care, the patient will restart X-396 (ensartinib) at the next lower dose level once toxicity has resolved to ≤ Grade 1.

Specific Recommendations for Drug-Related Liver Function Test Abnormalities:

For patients with Grade 3 liver enzyme elevations (AST/ALT) thought related to X-396 (ensartinib), X-396 (ensartinib) should be held until the values recover to ≤ Grade 1. Patients with an elevation of ALT ≥ 3 x ULN in conjunction with a bilirubin ≥ 2 x ULN may remain in the study if a correctable, non-drug related cause of the liver test evaluations can be documented; otherwise, the patient must be discontinued from the trial.

Specific Recommendations for Drug-Related Pneumonitis:

For pneumonitis of any grade not attributable to other causes, such as NSCLC progression, other pulmonary disease, infection, or radiation effect, trial treatment must be discontinued.

Table 5 Dose Modifications for Drug-Related Non-Hematologic Toxicities

Toxicity Grade	X-396 (ensartinib) Dose Modification
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 [a]
If Grade 3 toxicity lasts ≤7 days and resolves to baseline or ≤ Grade 1	Reduce one dose level [c]
Grade 3 and not expected to be manageable and reversible with dose reduction (e.g., cardiac failure)	Discontinue study drug
Recurrence of Grade 3 toxicity	Reduce one dose level or discontinue treatment [a, c]
Elevated ALT ≥3 x ULN in conjunction with a bilirubin ≥2 x ULN, and no correctable, non-drug related cause	Discontinue study drug
Grade 4	Discontinue study drug [a]
Pneumonitis of any grade [b]	Discontinue study drug

[a] X-396 (ensartinib) should be held until toxicity resolves to baseline or ≤ Grade 1. Any patient who develops toxicity that does not resolve to baseline or ≤ Grade 1 within 4 weeks should be removed from the trial treatment. 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 treatment with ensartinb, this may be allowed after discussion with the Medical Monitor.

[b] For pneumonitis of any grade not attributable to other causes, such as NSCLC progression, other pulmonary disease, infection, or radiation effect, discontinue study drug.

[c] For dose levels for expansion cohort phase, see Table 3.

9. TRIAL ASSESSMENTS AND TREATMENT

9.1. Overview

All patients will take X-396 (ensartinib) orally as a capsule formulation. The dosing frequency will initially be once daily, although if it is subsequently determined that it is appropriate to evaluate twice daily dosing, that will be permitted. In order that sufficient PK data are collected at doses below the MTD, additional patients may be enrolled at lower dose levels during the accelerated titration and/or 3+3 dose escalation phases.

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 X-396 (ensartinib) dosing. Priority should be given to PK collection at the time specified. Vital signs and ECG assessments should be performed prior to specimen collections.

All patients should visit the study center on the days specified within this protocol. 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 ≤7 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 should be performed ≤28 days prior to initiation of treatment.

9.3. Trial Treatment Period

Patients will visit the study center on Day 1 of each cycle (i.e., every 28 ± 3 calendar days) and at other times as specified. **Note that as of Amendment 9, after 12 months, if the patient has been stable or responding to X-396 (ensartinib), the investigator will have the discretion to reduce the frequency of the visits to every other cycle (with the understanding that the frequency may be adjusted back to every cycle if needed).** The visits may be scheduled to occur on the first day of the odd cycles, to coincide with the response assessments. 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 X-396 (ensartinib) 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 adverse events (AEs) for 30 calendar days after the last dose of trial drug.

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. If a patient withdraws from treatment during Cycle 1 due to any reason other than DLT and does not meet the minimum requirements for inclusion in the MTD-determining population described in

Section 7.1.4, that patient will be replaced if needed to have enough patients evaluated for a decision on dose escalation.

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.

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 12.1.1).

9.6.2. Laboratory Tests

9.6.2.1. CBC plus Differential and Platelets

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

- glucose
- blood urea nitrogen (BUN)
- creatinine
- sodium
- potassium
- magnesium
- chloride
- calcium
- carbon dioxide (CO_2)
- alkaline phosphatase
- AST (SGOT)
- ALT (SGPT)
- total bilirubin

- total protein
- albumin
- lactate dehydrogenase (LDH)
- phosphorus
- uric acid

9.6.2.3. Coagulation Measurements

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

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

As of Amendment 9, these tests will be obtained only at screening/baseline.

9.6.2.4. Testosterone Monitoring

Total testosterone levels will be monitored in male patients. **As of Amendment 9, this will be obtained only at screening/baseline.**

9.6.2.5. Urinalysis

A urine dipstick or other appropriate method for urinalysis (pH, specific gravity, blood, protein, glucose) will be performed. **As of Amendment 9, this will be required only at screening/baseline**. If abnormalities are present, additional testing (e.g., microscopic examination, etc.) should be done as clinically indicated.

9.6.2.6. Serum or Urine Pregnancy Test

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.

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), Philadelphia, PA. **As of Amendment 9, the requirement for triplicate ECGs read centrally by ERT is no longer required. However, ECGs will still be obtained at each visit to be read at the site for safety purposes.**

9.6.3.2. Ophthalmology Examination

An ophthalmology examination will be performed by an ophthalmologist at screening (within 28 days prior to treatment) for all patients and will be repeated when clinically indicated. **Note that, as of Amendment 9, eye exams are no longer required.**

The assessment should include:

- history of eye disease
- eye symptoms questionnaire to be filled out by the ophthalmologist
- prior and current ocular medications
- visual acuity (LogMAR)
- eye movements
- visual field by confrontation
- slit lamp examination
- funduscopic examination

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. Patients with progressive disease or unacceptable toxicity should be discontinued from the trial unless otherwise noted in the protocol; patients with stable disease or response to therapy will continue treatment. The assessments that will be performed at each visit during the trial treatment period are specified in Appendix E.

9.6.4.2. Cerebrospinal Fluid

For patients in the leptomeningeal disease cohort, CSF will be obtained at Screening, Cycle 2 Day 1, Cycle 3 Day 1, and then approximately every 8 weeks, or sooner, if clinically indicated/disease progression is suspected, and at the end of trial treatment (Appendix E). **Note that, as of Amendment 9, the leptomeningeal disease cohort is closed.**

9.6.4.3. Tumor Markers

If appropriate for tumor type, tumor markers (e.g., CEA, CA 19-9, CA 125, CA 15-3) will be assessed.

9.7. Pharmacokinetic Assessments

The plasma PK parameters (including $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$, C_{max}, t_{max}, λ_z, and $t_{½}$) of X-396 (ensartinib) following oral administration will be assessed by analysis of blood samples.

Dose Escalation Phase:

During treatment in the dose escalation phase, PK blood samples will be taken at approximately the following time points:

- **Cycle 1 Day 1** (note that for patients receiving BID dosing, this should be in conjunction with first dose only): pre-dose, and at 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours. In addition to these time points, only patients receiving BID dosing should have a 12 hour sample, obtained prior to the 2nd dose. Only patients receiving QD dosing should have a 24 hour post-dose sample (Day 2), obtained prior to the next dose.
- **Cycle 1 Day 8:** pre-dose
- **Cycle 1 Day 15:** pre-dose
- **Cycle 1 Day 22** (note that for patients receiving BID dosing, this should be in conjunction with first dose only): pre-dose, and at 30 minutes, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours.

Expansion Cohort Phase:

- For the expansion cohort phase, PK sampling should be obtained from as many patients as possible. **As of Amendment 9, only sparse PK sampling should be obtained.** These samples should be collected pre-dose and approximately 3-4 hours 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. Patients will be asked to record the time that they took their last dose of study medication on the day before their scheduled visit.

Note: An unscheduled 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

One EDTA tube will be collected at baseline from as many patients as possible for possible future testing.

See Laboratory Manual for handling and shipping instructions.

9.9. Biomarkers

The analyses for biomarkers are exploratory, and will not be used to guide treatment decisions. The results may be pooled with data from other studies to generate hypotheses to be tested in future studies.

9.9.1. Assessment of Tumor Tissue Samples

Patients entering this study will be asked to provide tissue (archival and/or fresh biopsy) for correlative testing. Submission of archival tissue and/or pre-treatment fresh tumor biopsy is encouraged; however, if it is not available or the patient refuses, the patient may still be eligible for enrollment. The pathology reports demonstrating ALK genomic alterations need to be sent to

the Medical Monitor for review. Additional on-study biopsies taken within 1 week prior to Cycle 2 Day 1 and/or at the time of disease progression are optional for patients in both portions of the study. See Laboratory Manual for handling and shipping instructions for the tissue samples. Informed consent must be obtained from any patient who agrees to provide tissue for correlative testing.

As of Amendment 9, the enrollment requirement for tissue testing as part of the study to demonstrate ALK genomic alterations by FISH or IHC has been removed. ALK TKI-naïve patients and patients with a known ALK 1198 mutation will be allowed to enroll based on local FDA-approved ALK results and patients who have received a prior ALK TKI(s) will be allowed to enroll based on having received prior treatment with crizotinib and/or a 2nd generation ALK TKI. All patients will be asked to provide a copy of the pathology report demonstrating ALK genomic alterations (including the 1198 mutation for patients in that cohort). For ALK TKI-naïve patients, if a pathology report documenting ALK genomic alterations is not available, a fresh tumor biopsy is required and the patient may be eligible once documented ALK-positive using an FDA-approved assay. Samples that are obtained may be evaluated centrally by approved or exploratory FISH assays, IHC, NGS and/or reverse transcription quantification polymerase chain reaction (RT-qPCR) on an exploratory basis.

9.9.2. Biomarker Blood Samples for ALK and MET and Treatment Response Testing

During treatment, biomarker blood samples (optional, but encouraged) will be taken for exploratory evaluation of nucleic acids (such as DNA, RNA) and/or proteins at the following time points for patients in the expanded cohort portion of the study):

- **Cycle 1 Day 1:** pre-dose
- **Day 1 of Each Cycle from Cycle 2** through End of Trial Treatment (for patients on the reduced frequency visits, biomarker samples will only be collected at cycles requiring a visit)
- **End of Trial Treatment**

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

9.9.3. Skin Biopsies and Photos

For patients that develop a rash thought to be related to X-396 (ensartinib), skin biopsies and digital photos of the rash are encouraged to develop a better understanding of the rash. See Laboratory Manual for handling and shipping instructions.

10. INVESTIGATIONAL PRODUCTS

Investigational Product	Dosage Form and Strength	Manufacturer
X-396 (ensartinib)	25 mg and 100 mg, capsules	Xcovery

X-396 (ensartinib) will be administered orally as hard capsules.

Additional information can be found in the X-396 (ensartinib) IB.

10.1. Labeling, Packaging, and Supply

X-396 (ensartinib) capsules will be supplied in 2 strengths: 25 mg and 100 mg

X-396 (ensartinib) capsules are packaged in HDPE bottles, each bottle is capped with child resistant induction seal caps. Thirty capsules are included in each bottle. No preparation of X-396 (ensartinib) is necessary.

Study drug will be labeled as required by all applicable regulations. All study drugs must be kept in a secure place under appropriate storage conditions. X-396 (ensartinib) capsules should be stored at room temperature, 15°C to 30°C (59°F to 86°F).

Upon patient enrollment, the clinical site pharmacist will dispense the study drug to the patient in accordance with the assigned dosage regimen/randomization schedule. Each bottle of 30 capsules should be sufficient for the patient's treatment until the next visit (and potential overage to maintain their dosing routine). **Note that, as of Amendment 9, after 12 months, if the visit frequency will be changed to every other cycle (see Section 9.3), the pharmacy may dispense up to two cycles of study drug at a time.** Any unused study drug must be returned to the site.

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

10.2. Preparation and Administration of Investigational Products

10.2.1. X-396 (ensartinib)

X-396 (ensartinib) will be self-administered 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.

10.3. Accountability of Investigational Products

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

The Novella Clinical 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, clinical trial supplies will be 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.

10.4. Precautions and Risks Associated with X-396 (ensartinib)

Refer to the IB for details of the risks associated with the use of X-396 (ensartinib).

11. RESPONSE EVALUATIONS AND MEASUREMENTS

11.1. Definitions

Response and progression for systemic disease will be evaluated in this trial using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Response and progression for CNS metastases will also be evaluated using criteria based on Response Assessment in Neuro-Oncology (RANO) Criteria, summarized and modified in a White Paper by Schmid et al (with some further modifications [e.g., target lesion may be ≥ 3 mm, rather than 5 mm]). Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by computerized tomography (CT) scan (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. (Note that for CNS metastases, "target lesions" must be 3 mm or greater in diameter as assessed by gadolinium-enhanced, T1-weighted brain MRI, and one should avoid selecting necrotic or cystic lesions as target lesions if other solid lesions are present). **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion. Photographs should be taken on confirmation that the lesion on skin biopsy is compatible with metastatic carcinoma and then monthly until lesion is gone or patient comes off protocol.

	Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the **short axis will be measured and followed**.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <10 mm [or <3 mm as assessed by gadolinium-enhanced, T1-weighted brain MRI for CNS metastases] or pathological lymph nodes with >10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging requirements.

11.1.1. Systemic Disease

Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion of a short axis of >15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

11.1.2. CNS Metastases

Target Lesions:	• Size: ≥3 mm in long axis • Avoid selecting necrotic or cystic lesions as target lesions if other solid lesions are present • Measure on axial plane, preferably post-contrast T1 • Slice selection: the slice with the longest in-plane diameter should be chosen at baseline for each target lesion's measurement • Maximum of 5 lesions in the brain • Calculate the sum of diameters (the sum of the longest axes of all target brain lesions)
Non-Target Lesions:	• Include all measurable lesions not chosen as target lesions • Lesions <3 mm in long axis • Multiple lesions in brain may be grouped together and assessed collectively • There is no limit on number of non-target lesions

11.2. Guidelines for Evaluation of Measurable Disease

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. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

11.2.1. Systemic Disease

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; CT is, however preferable.

Conventional CT and MRI:	CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness, contiguously. Spiral CT scan should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
Ultrasound:	When the primary trial endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
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).

11.2.2. CNS Metastases

MRI:	Slice thickness with a maximum of 3 mm (1.5 mm preferred) T1 pre- and post-contrast. If a target lesion separates to form discrete lesions on a subsequent imaging timepoint, longest diameter of each lesion should be calculated and reported separately.

11.2.3. Response Criteria

11.2.3.1. Systemic Disease

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters 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.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<10 mm short axis).
Stable Disease (SD):	Persistence of one or more non-target lesions not meeting the criteria for PD 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. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. It must be representative of overall disease status change, not a single lesion increase. When the patient also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

Overall response will be assessed at each post-baseline assessment time point and will be derived from the contribution of the target lesions response, the non-target lesions response and the

presence or absence of new lesions. Overall response should take into account systemic and CNS lesions, if applicable. CNS response will also be assessed separately, if applicable.

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.

If a lesion disappears and reappears at a subsequent time point, it should continue to be measured. The patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. The reappearance of an apparently 'disappeared' single lesion amongst many which remain may not be enough to qualify for PD.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). 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.

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

The best overall response during the course of the study is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. For patients with CNS lesions, in addition to the best overall response, an assessment will be made for CNS disease response, as described below.

Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for trials in which response rate is the primary endpoint, but is not required in randomized trials or trials with primary survival endpoints (i.e., where response is not a primary endpoint).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

11.2.3.2. CNS Metastases

Evaluation of Target Lesions

Complete Response (CR):	Absence of all lesions and the entire brain is evaluable. CR is also achieved when all target lesions do not show any gadolinium enhancement but are completely necrotic.
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter of target lesions from baseline.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of longest diameter since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the longest diameter 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, with or without worsening of neurological symptoms.
Not Evaluable (NE):	Incomplete imaging or change in modality preventing precise measurement.

Evaluation of Non-Target Lesions

Complete Response (CR):	Absence of all non-target lesions and all lesions are evaluable. CR is also achieved when all non-target lesions do not show any gadolinium enhancement but are completely necrotic.
Non-CR/Non-PD:	Persistence of one or more non-target lesions and does not meet criteria for PD or NE.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions, with or without worsening of neurological symptoms.
Not Evaluable (NE):	Incomplete imaging or other causes preventing assessment of lesions and no lesions are PD.

New Lesions

Equivocal:	New lesion is definitely present but may not represent malignancy, or a new lesion which may be present but is either too small, too ill-defined to be certain, or is a potential artifact. Equivocal lesions do not trigger PD at the current timepoint. If an equivocal lesion becomes unequivocal at a later timepoint, the time of progression is dated back to the timepoint of that lesion's first recognition. Equivocal new lesions prevent an overall assessment of CR
Unequivocal:	Lesion which is considered new and malignant, that is not attributable to differences in scanning technique or findings, irrespective of its size. Unequivocal new lesions trigger PD.
Special Circumstances:	New significant edema with a mass effect if it corresponds to a gadolinium-enhancing lesion or leptomeningeal disease is considered new lesion. Lesions detected in areas not scanned/documented at baseline will be considered unequivocal new lesions and will trigger PD. Hemorrhage is not a non-target lesion and is not a new lesion.

Evaluation of Best Overall Response for CNS Metastases

Overall CNS response will be assessed at each post-baseline assessment time point and will be derived from the contribution of the CNS target lesions response, the CNS non-target lesions response and the presence or absence of new CNS lesions.

The best overall response for CNS metastases is the best response recorded from the start of the treatment until CNS disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

CNS Target Lesions	CNS Non-Target Lesions	CNS New Lesions	CNS Overall Radiological 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 (unequivocal) or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

12. SAFETY REPORTING AND ANALYSES

12.1. 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.

12.1.1. 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 (SAR) means any AE for which there is a reasonable possibility that the drug caused the AE. 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 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.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).

12.1.2. 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 X-396 (ensartinib) treatment (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 X-396 (ensartinib) do not have to be reported.

12.1.3. Abnormal Laboratory Values and Vital Signs

The reporting of abnormalities of vital signs as AEs should generally be avoided. Abnormalities of vital signs should not be reported unless 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.

12.1.4. 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.

12.2. Serious Adverse Events

12.2.1. 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 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 Novella Clinical 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.

12.2.2. Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to Novella Clinical in order to comply with regulatory and any other applicable competent authority 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 Novella Clinical 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 Novella Clinical 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 study manual.

Investigators must report SAEs and follow-up information to their responsible IRB/EC according to the policies of the responsible IRB/EC.

Contact details for the Novella Clinical Safety Department are as follows:

Novella Safety Department

Phone: 1-866-758-2798
Fax: 1-866-761-1274
Email: pvgsafety@novellaclinical.com

12.2.3. 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 SAR 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 FDA and all participating investigators in a written IND safety report of any SAR 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 SAR.

The Sponsor or designee will notify FDA and all participating investigators in a written IND safety report of any fatal or life-threatening SAR 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 Sponsor will identify all safety reports previously filed with the IND concerning a similar SAR, and will analyze the significance of the SAR in light of the previous, similar reports.

12.3. 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 12.2.2.

12.3.1. 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.

12.3.2. 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.

12.3.3. 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.

12.3.4. Deaths

For this protocol, observation of the clinical and laboratory AEs produced by X-396 (ensartinib) 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 Novella Clinical 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.

12.3.5. 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 12.2.1).

12.3.6. 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.

12.3.7. Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to Section 12.4 for specific instructions.

12.3.8. 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 12.2.1). 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.

12.3.9. 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.

12.4. Protocol-Defined Events of Special Interest

The following are events of special interest, and will need to be reported expeditiously (see Section 14.1):

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 Novella Clinical Safety Department. The Novella Clinical 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 Novella Clinical 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 dose-limiting toxicity (see Section 7.1.3) or clinically significant ECG abnormalities should be reported immediately.

X-396 (ensartinib) 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 12.2.2).

Overdose information for X-396 (ensartinib) is not available.

For additional information, see the IB.

13. STATISTICAL CONSIDERATIONS

13.1. Statistical Design

This is an open-label, Phase I/II, first in human (FIH), dose-escalation study of the ALK/MET inhibitor X-396 (ensartinib), with expansion cohorts at or below the MTD. This trial is designed to determine the MTD (or recommended dose based on available safety, PK, and response data) in support of dose determination for further clinical studies, and preliminary information on the safety profile, PK profile, and biological and anti-tumor activity of X-396 (ensartinib) given as a single agent in patients with advanced solid tumors. Tumor response will be evaluated by the investigator.

Safety and PK data will be examined on an ongoing basis while the study is being conducted.

This trial will enroll up to 190 patients and may include up to 50 sites, 24 of which will be in the US. Global sites may be initiated for the expansion phase of the study only. It is anticipated that approximately 6 dose cohorts will be evaluated during the trial. However, the actual number of dose cohorts explored will depend upon the MTD and the safety profile observed during the conduct of the trial.

13.2. Data Analyses

13.2.1. Safety Analyses

The safety endpoints to be summarized are:

- Incidence of DLTs (see Section 7.1.3)
- Incidence of AEs and AEs considered to be drug-related
- Incidence of Grade 3 and Grade 4 AEs
- Incidence of SAEs
- Laboratory values
- ECGs/vital signs
- Protocol defined events of special interest (see Section 12.4)

In addition, the PK of X-396 (ensartinib) may be evaluated with respect to AEs considered to be drug-related to determine if a relationship between these might exist, and gender differences in toxicity may be evaluated.

The safety endpoints will be listed and/or summarized by dose cohort. No inferential statistical analyses will be performed.

All patients who have received at least one dose of X-396 (ensartinib) will be included in the safety population.

13.2.2. Pharmacokinetic Analyses

The primary PK endpoints are $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$, C_{max}, t_{max}, λ_z, and $t_{½}$. Other relevant parameters (e.g., accumulation ratio) will also be calculated from the data reported.

The PK parameter estimates will be used to evaluate dose proportionality and the predictability of the multiple dose PK from single dose data, provided sufficient data exist. In addition, potential gender differences in PK will be evaluated.

Blood will be collected from all treated patients for measurement of X-396 (ensartinib) in plasma concentration for PK analysis (see Section 9.7 and Appendix E). The plasma concentration data will be summarized by dose cohort in tables of mean, standard deviation, median, and range over time. The PK parameters will be estimated for each patient, and descriptive statistics will be calculated for each dose cohort. Correlation of C_{max} and AUC with dose will also be evaluated. Accumulation will be assessed by comparing multiple dose PK data to single dose data.

13.2.3. Tumor Response

The number of patients with complete responses, partial responses, stable disease, and progressive disease for each dose/expansion cohort and tumor type/population or prior treatment cohort (e.g., crizotinib-naïve, prior crizotinib failures, etc.)/genomic alterations (e.g., ALK-positive, ALK-negative, MET status as confirmed centrally), and presence of baseline CNS metastases or leptomeningeal disease will be listed and summarized, if appropriate. Tumor response will be evaluated by the investigator. While central testing for ALK will be performed, patients in the expansion cohort phase may be deemed to be evaluable with respect to ALK status based on local results if there could not be a central read or there are questions about the accuracy of the central read based on the adequacy of the tissue specimen. **Note that with Amendment 9, central testing for ALK will no longer be required.** The endpoints for tumor response are:

- Proportion of patients with an overall tumor response (CR + PR)
- Duration of response
- Proportion of patients with SD
- Time to disease progression (TTP) and progression-free survival (PFS)
- CNS response rate (for patients with CNS lesions at baseline)
- Time to CNS progression.

The overall tumor response will be reported descriptively. Exact 90% and 95% confidence intervals will be constructed for overall response rates.

13.3. Statistical Methods

Data will be listed and/or summarized and tabulated. Descriptive statistics such as mean, median, standard deviation, maximum, and minimum for continuous variables, and counts and percentages for discrete variables, will be used to summarize data. Exact 90% and 95% confidence intervals will be constructed to describe response rates.

13.3.1. Interim Analysis

No formal interim analysis is planned for this study.

13.3.2. Power and Sample Size Determination

This study will enroll up to 190 patients. The number of patients treated will depend upon the need to expand the escalation cohorts from 3 to 6 based on toxicity, the total number of cohorts treated before DLT is observed and the MTD is determined, and the number of additional patients enrolled in the expanded cohort phase.

Initially, this sample size was not chosen based on statistical considerations or to obtain adequate power for a particular endpoint analysis, but was chosen to allow for providing a preliminary safety and PK assessment of X-396 (ensartinib). As of Amendment 8, promising response rates were observed during the Phase II expansion cohort phase that were within the range of historical controls for other agents. **As of Amendment 9, to improve the precision of the estimated response rates and to gain more experience with X-396 (ensartinib) in these patient populations, the sample size for selected expansion cohorts was increased, to up to 25 patients for the ALK TKI-naïve cohort, up to 40 patients for the cohort including patients that progressed on prior crizotinib and did not receive another ALK TKI, and up to 50 patients for the cohort including patients that progressed on a 2nd generation ALK TKI.** An increase to 40 patients would allow cohort response rates to be estimated within no worse than +/- 15% with 90% confidence. An increase to 50 patients would allow cohort response rates to be estimated within no worse than +/- 12% with 90% confidence. **In addition, as of Amendment 9, because of interest in the ALK 1198 mutation, a cohort for patients whose tumor is known to have that mutation is being opened, with up to 20 patients allowed in that cohort.**

ALK+ Expansion Cohort	(CR+PR) / Evaluable Patients (%) (ongoing)	Response Rate (CR+PR) in Historical Control*	Original Cohort Sample Size	New Cohort Sample Size
Pts who progressed on prior crizotinib and have not received other ALK TKIs	8/12 (75%)	~50%	15	30
Pts who progressed on at least one 2nd generation ALK TKI (pts may or may not have also received prior crizotinib)	2/8 (25%)	Unknown	15	30
Pts with CNS metastases	4/7 (57%)	57%	10	30
X-396 (ensartinib) data from February 2016 Custom Listings * Response rates by investigator assessment, Alecensa 2015 and Zykadia 2014 Prescribing Information				

13.4. Data and Safety Monitoring Board

The trial will not utilize the services of a Data Safety Monitoring Board (DSMB). However, an internal Safety Review Team will review the safety data from the trial at least quarterly as noted in the Safety Monitoring Plan for the study.

13.5. Steering Committee

The trial will not utilize the services of a Steering Committee.

14. 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 and patient feel it is in the patient's best interest to remain on study treatment, they may be allowed to continue after discussion with the Medical Monitor.
- Intolerable drug-related toxicity (see Sections 7.1.3 and 8)

- Patient requests to discontinue treatment/withdraw from the trial (withdrawal of consent)
- Pregnancy (see Section 14.1.)
- 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)
- Lost to follow-up
- Discontinuation of the study by the Sponsor

If a patient withdraws from treatment during Cycle 1 due to any reason other than DLT and does not meet the minimum requirements for inclusion in the MTD-determining population described in Section 7.1.4, that patient will be replaced if needed to have enough patients evaluated for a decision on dose escalation.

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.

14.1. Pregnancy

During the course of the trial, all female patients 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 or the partner of a male

patient becomes pregnant while enrolled in the trial, a Pregnancy Form should be completed and submitted to the Novella Clinical Safety Department. For more details regarding handling and reporting of pregnancies that occur during treatment, see Section 12.3.7.

15. 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. 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.

16. CLINICAL MONITORING

16.1. 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 Clinical Monitoring Plan shall define aspects of the monitoring process.

17. 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).

17.1. IRB/EC 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/EC 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/EC trial review. The PI/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IRB/EC 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/EC.

Safety updates for X-396 (ensartinib) will be prepared by the Sponsor or its representative, as required, for submission to the relevant IRB/EC.

17.2. 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 X-396 (ensartinib) will be prepared by the Sponsor or its representative, as required, for submission to the relevant regulatory authority.

17.3. Insurance and Indemnity

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

17.4. 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/EC 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 specfic 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.

17.5. Confidentiality

17.5.1. 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 sequentially at each site by number only; the 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/EC 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.

17.5.2. Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the SCRI Innovations and Novella Clinical database(s), 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, SCRI Innovations and Novella Clinical shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

17.6. 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 21 CFR Part 54 and local regulatory authorities shall be appropriately provided.

18. RECORD RETENTION AND DOCUMENTATION OF THE TRIAL

18.1. 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/EC(s) for the board's approval.

Items requiring a protocol amendment with IRB/EC 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.

18.2. 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 Novella Clinical.

18.3. 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, where appropriate.

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, 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/EC 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.

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

According to ICH E6 4.9, all CRFs, as well as supporting documentation and administrative records, must be retained by the Investigator for a minimum of 2 years following notification that the appropriate regulatory authority has approved the product for the indication under study, notification that the entire clinical investigation will not be used in support of a marketing application, or notification that the marketing application was not approved.

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.

18.4. 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 Novella 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.

18.5. 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.

18.6. 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.

18.7. Disclosure and Publication Policy

All information provided regarding the trial, as well as all information collected/documented during the course of the trial, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the trial. Results from the trial will be published/presented as per the Sponsor's publication strategy.

The financial disclosure information will be provided to the Sponsor prior to trial participation from all PIs and sub-investigators who are involved in the trial.

Inclusion of the investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the trial. The investigator acknowledges that the trial is part of a multicenter trial and agrees that any publication by the investigator of the results of the trial conducted at his/her research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the trial has been completed or terminated at all trial sites, and all data have been received, the investigator shall have the right to publish his/her results from the trial, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. The investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the trial for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the Sponsor requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any site confidential information from the publication.

A Confidentiality Disclosure Agreement (CDA) shall be executed between the Sponsor and study site and/or the PI. The document shall address areas of confidentiality, like patents that may result as part of the trial, but it is intended to address confidentiality of the protocol, the drug, and its findings/results.

A Clinical Trial Agreement (CTA) shall be executed between the Sponsor and the PI. The document shall address any offers, especially monetary offers, by the Sponsor to the PI for services/results with acceptance by all involved.

19. 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 ALK-positive patients with non-small cell lung cancer (NSCLC). J Clin Oncol 2010; 28: suppl; abstract 3.

Chamberlain et al. 2014

Chamberlain MC, Junck L, Brandsma D, et al. Leptomeningeal metastases: A rano proposal for response criteria. J Clin Oncol 2014; 32 (suppl: abstr e13019).

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.

FDA Guidance 2005

FDA Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, July 2005.

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 et al. 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.

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.

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.

Schmid et al. 2014

Schmid A, Bohnsack O, Jacobs R. White Paper on brain metastases from solid tumors: implementing response assessments. June 2014.

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 EML4-ALK 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.

20. 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 at least 90 days (women) or 90 days (men) following discontinuation of X-396 (ensartinib). Male patients must also refrain from donating sperm for 90 days following discontinuation of X-396 (ensartinib).

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. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) 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 with Known Risk of Torsades De Pointes

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

Amiodarone (Cordarone® and others)	Ibutilide (Corvert®)
Anagrelide (Agryline® and others)	Levofloxacin (Levaquin® and others)
Arsenic trioxide (Trisenox®)	Levomeprazine (Nosinan® and others)
Astemizole (Hismanal®)	Levomethadyl acetate (Orlaam®)
Azithromycin (Zithromax® and others)	Levosulpiride (Lesuride and others)
Bepridil (Vascor®)	Mesoridazine (Serentil®)
Chloroquine (Aralen®)	Methadone (Dolophine® and others)
Chlorpromazine (Thorazine® and others)	Moxifloxacin (Avelox® and others)
Cilostazol (Pletal®)	Ondansetron (Zofran® and others)
Ciprofloxacin (Cipro® and others)	Oxaliplatin (Eloxatin®)
Cisapride (Propulsid®)	Papaverine HCl (intra-coronary)
Citalopram (Celexa® and others)	Pentamidine (Pentam®)
Clarithromycin (Biaxin® and others)	Pimozide (Orap®)
Cocaine (Cocaine)	Probucol (Lorelco®)
Disopyramide (Norpace®)	Procainamide (Pronestyl® and others)
Dofetilide (Tikosyn®)	Propofol (Diprivan® and others)
Domperidone (Motilium® and others)	Quinidine (Quinaglute® and others)
Donepezil (Aricept®)	Roxithromycin (Rulide® and others)
Dronedarone (Multaq®)	Sevoflurane (Ulane® and others)
Droperidol (Inapsine® and others)	Sotalol (Betapace® and others)
Erythromycin (E.E.S.® and others)	Sparfloxacin (Zagam®)
Escitalopram (Cipralex® and others)	Sulpiride (Dogmatil® and others)
Flecainide (Tambocor® and others)	Sultopride (Barnetil and others)
Fluconazole (Diflucan® and others)	Terfenadine (Seldane®)
Gatifloxacin (Tequin®)	Terlipressin (Teripress and others)
Grepafloxacin (Raxar®)	Terodiline (Micturin® and others)
Halofantrine (Halfan®)	Thioridazine (Mellaril® and others)
Haloperidol (Haldol® (US & UK) and others)	Vandetanib (Caprelsa®)
Ibogaine	

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-101[w]

Procedures	Pre-Treatment	Cycle 1 *Cycle = approx. 28 days*		Cycle 2	Cycle 3 Through End of Treatment		End of Trial Treatment[s]
	Screening/ Baseline	Day 1 (pre-dose)	Day 15	Day 1[u]	Every 2 Cycles (*Every 8 Wks*)[u]	Day 1 (*Every 4 Weeks*)[u]	
TESTS & OBSERVATIONS							
Informed Consent[a]	X[a]						
Medical history (including smoking history)	X						
Physical examination including whole body skin exam, neurologic exam for patients with CNS mets, vital signs, height, weight[c]	X	X[b]	X	X		X	X
ECOG Performance Status	X	X[b]		X		X	X
Adverse event evaluation	X	X	X	X		X	X
Concomitant medication review	X	X	X	X		X	X
LABORATORY TESTS							
CBC, including differential and platelets[d]	X	X[b]	X	X		X	X
Chemistry[e]	X	X[b]	X	X		X	X
Coagulation tests[f,b]	X						
Total testosterone[g]	X						
Ophthalmology examination[h]							
12-lead ECG[i]	X	X		X		X	X
Urinalysis[j,b]	X						
Serum or urine pregnancy test[k]	X						X
PK blood[l]		X		X[l]	X[l]		X[l]
Biomarker blood sample collection[t]		X		X		X	X
PG blood sample[m]	X						
Tumor tissue sample[p]	X			X[p]			X[p]
DISEASE ASSESSMENT							
CT scan of the chest, abdomen, pelvis[n,r]	X				X		X
MRI brain[o,r]	X			X[o]	X		X
Tumor markers (if applicable)[q]		X		X		X	

Appendix E: Schedule of Assessments for Protocol X396-CLI-101 (continued)

a. Informed Consent must be obtained ≤28 days prior to the initiation of trial treatment.
b. The screening physical examination, ECOG performance status, hematology, blood chemistry, coagulation, and urinalysis tests should be done ≤7 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. Note that the screening coagulation and urinalysis tests do not have to be obtained within 72 hours of Cycle 1 Day 1 or repeated on Cycle 1 Day 1.
c. Physical examinations will include measurements of weight and vital signs (resting heart rate, blood pressure, respiratory rate, temperature [preferably oral, but other methods may be used, if necessary]). Physical examinations will also include a whole body skin examination. For patients with CNS metastases, neurologic exam should be included. Note that vital signs should be assessed before blood collection. At the screening visit only, height will also be recorded. Note that patients that develop a skin rash thought to be related to X-396 (ensartinib) 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. Physical examinations will be done on Day 1 of each cycle; during Cycle 1 only, patients will have an additional abbreviated physical exam done on Day 15.
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.
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, LDH, phosphorus, uric acid.
f. As of Amendment 9, coagulation tests, which include PT/PTT/INR, will be obtained only at screening/baseline.
g. As of Amendment 9, total testosterone will be collected from male patients only at screening/baseline.
h. As of Amendment 9, eye exams are no longer required.
i. **As of Amendment 9, the requirement to obtain triplicate ECGs with central reading by ERT is removed.** 12-lead ECGs will be collected at the screening visit, pre-dose on the Day 1 visit of each treatment cycle, and at the End of Trial Treatment visit. These will be read at the site for safety purposes. Note that ECGs should be obtained before blood collection.
j. **As of Amendment 9, urine dipstick or other appropriate method for urinalysis (pH, specific gravity, blood, protein, glucose) will be done only at screening/baseline.** If abnormalities are present, additional testing (e.g., microscopic examination, etc.) should be done as clinically indicated.
k. 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 (see Section 9.6.2.6).
l. **As of Amendment 9, full PK sampling is not required.** Sparse PK blood samples (see Section 9.7) should be obtained from as many patients as possible. These samples should be collected pre-dose and approximately 3-4 hours 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. Patients should be asked to record the time that they took their last dose of study medication on the day before their scheduled visit.
m. One optional **(as of Amendment 9)** pharmacogenetic blood sample (one EDTA tube) will be collected at baseline from as many patients as possible for possible future testing.
n. 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.
o. **All patients enrolled under Amendment 9 must have a gadolinium-enhanced, T1-weighted MRI of the brain at screening/baseline (unless there is a contraindication for MRI, in which case CT with and without contrast may be used).** These scans should be performed ≤28 days prior to initiation of treatment. In patients with a positive scan at baseline, restaging will be done approximately every 8 weeks,whenever CNS progression is suspected, and at the End of Trial Treatment visit. In patients with a negative scan at baseline, a follow-up scan should be obtained as clinically indicated. Repeat scans should use the same method as that used at baseline.
p. Pre-treatment tumor sample (archival tissue and/or fresh biopsy) is encouraged, if available, for patients in the dose escalation and dose expansion portions of the study. **As of Amendment 9, for ALK TKI-naïve patients, if a pathology report documenting ALK genomic alterations is not available, a fresh tumor biopsy is required and the patient may be eligible once documented ALK-positive using an FDA-approved assay.** Note that a biopsy that had been obtained within 60 days prior to the start of treatment may be utilized to provide ALK results if no other anticancer therapy was given after the biopsy and before the start of study treatment. Additional on-study

biopsies taken within 1 week prior to Cycle 2 Day 1 and/or at the time of disease progression are optional for patients in both phases of the study. ALK alterations may be assessed locally or centrally by an FDA approved ALK assay. Mutational analysis may also be performed. If additional slides or tissue are available, exploratory FISH, NGS and IHC analyses may be performed. Note that patients that develop a skin rash thought to be related to X-396 (ensartinib) 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. If appropriate for tumor type, tumor markers (e.g., CEA, CA 19-9, CA 125, CA 15-3) will be assessed on Cycle 1 Day 1 or ≤28 days of initiation of trial treatment, and on Day 1 of each treatment cycle thereafter.

r. Patients will be assessed according to RECIST v1.1 criteria (and CNS lesions will also be assessed by modified RANO). Assessments by CT or MRI will be performed after every even cycle of treatment. All assessments should be performed within 7 days of the scheduled day of assessment. Tumor lesions followed on physical examination must be assessed on Day 1 of each cycle and at the End of Trial Treatment visit.

s. 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 for 30 calendar days after the last dose of study drug.

t. Optional (but encouraged) biomarker blood samples for exploratory evaluation of nucleic acid (such as DNA, RNA) and/or protein will be obtained for patients in the expanded cohort portion of the study. In addition to testing for ALK and/or MET, other resistance mechanisms may be evaluated. Approximately 10 mL of blood will be obtained in each of 2 cell-free DNA BCT 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.

u. Day 1 of each cycle after the first should occur 28 days ± 3 days after Day 1 of the prior cycle. If the patient has been on study treatment for 12 months and is stable or responding to X-396 (ensartinib), the PI will have the discretion to reduce the frequency of the visits to every other cycle (with the understanding that the frequency may be adjusted back to every cycle if needed). The visits may be scheduled to occur on the first day of the odd cycles, to coincide with the response assessments. In addition, the pharmacy may dispense up to two cycles of study drug at a time.

v. As of of Amendment 9, the leptomeningeal disease cohort will be closed.

w. As of Amendment 9, no visits or assessments will be required for C1D2, C1D8, C1D22, and C2D15.