CLINICAL STUDY PROTOCOL

Protocol Title: A Randomized, Three-Arm, Open-Label Phase 3b Clinical Trial of Aumolertinib, versus Aumolertinib with Chemotherapy, versus Osimertinib for Patients with Metastatic NSCLC and an EGFR Mutation (TREBLE)

Protocol Number: EQ143-301

Compound: aumolertinib (EQ143)

Brief Title: Aumolertinib with Chemotherapy or Alone Compared with Osimertinib in Patients with Epidermal Growth Factor Receptor-Mutant Non-Small Cell Lung Cancer

Study Phase: Phase 3b

Sponsor Name: EQRx International, Inc.

Legal Registered Address:

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Cambridge, MA 02139 USA

Regulatory Agency Identifier Number(s):

US: [redacted]

CTIS: [redacted]

EU: [redacted]

NCT Number: NCT05493501

Protocol Version and Date: Version 6.0 (Amendment 5), 19 May 2023

Confidentiality Statement

SPONSOR SIGNATORY

As representative of the Sponsor, EQRx International, Inc., I confirm that this study protocol was subjected to critical review. The information contained herein is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the relevant law and any amendments thereof and in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

I confirm that the following protocol has been agreed to and accepted. The Sponsor will collect the signed Investigator's Agreement page of the protocol, in which each Investigator agrees to conduct the trial in compliance with the approved protocol and adhere to the principles outlined in the current ICH GCP Guidelines and any subsequent amendments thereof; the Sponsor's (and any other relevant) standard operating procedures; and all applicable regulatory requirements in the countries where the study is conducted and any subsequent amendments thereof.

I also confirm that the Sponsor will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay, and that an honest, accurate, and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
[redacted] 9:31:47 PM EDT
[redacted]

5/21/2023

Date

DOCUMENT HISTORY	
Document	**Date**
Amendment 5 (v6.0)	19 May 2023
Amendment 4 (v5.0)	10 April 2023
Amendment 3 (v4.0)	13 December 2022
Amendment 2 (v3.0)	01 July 2022
Amendment 1 (v2.0)	22 June 2022
Original Protocol (v1.0)	09 February 2022

INVESTIGATOR'S AGREEMENT

Protocol Title: ***A Randomized, Three-Arm, Open-Label Phase 3b Clinical Trial of Aumolertinib, versus Aumolertinib with Chemotherapy, versus Osimertinib for Patients with Metastatic NSCLC and an EGFR Mutation (TREBLE)***

All documentation for this study that is supplied to me and has not previously been published will be kept in the strictest confidence. Documentation includes, but is not limited to, the study protocol, Investigator's Brochure(s), electronic case report forms, and other scientific data.

The study will not commence without the approvals and/or registrations as required in the countries where the study is conducted. No changes will be made to the study protocol without the prior written approval of the Sponsor, Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and all other applicable approvals as required in the countries where the study is conducted, except where necessary to avert an immediate hazard to the study participants.

I have read the protocol and agree that the study will be conducted in compliance with the protocol and in accordance with the principles outlined in the current ICH GCP Guidelines and any subsequent amendments thereof; the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928), and any subsequent amendments thereof; the current Guideline for GCP E6 (R2) (European Medicines Agency/Committee for Medicinal Products for Human Use/ICH/135/1995) and any subsequent amendments thereof; the current clinical trial regulations in the countries where the study is conducted and any subsequent amendments thereof; the Sponsor's (and any other relevant) requirements; and all applicable regulatory requirements in the countries where the study is conducted and any subsequent amendments thereof. The conduct of the study will be in accordance with the Integrated Addendum to ICH E6 (R1): Guideline for GCP ICH E6 (R2) and any subsequent amendments thereof.

I acknowledge that I am responsible for the overall study conduct. I agree to personally conduct or supervise the described clinical study. I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study at my site are informed about their obligations. Mechanisms are in place to ensure that site staff receive the appropriate information throughout the study.

_____
Investigational Site

_____
Printed Name of Investigator

_____
Signature of Investigator

_____
Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document Version	**Date**
Version 6.0 (Amendment 5)	19 May 2023
Version 5.0 (Amendment 4)	10 April 2023
Version 4.0 (Amendment 3)	13 December 2022
Version 3.0 (Amendment 2)	01 July 2022
Version 2.0 (Amendment 1)	22 June 2022
Version 1.0 (Original Protocol)	09 February 2022

Version 6.0 (Amendment 5): 19 May 2023

Version 6.0 (Amendment 5) of this Phase 3b study protocol is considered to be a nonsubstantial protocol amendment because it does not impact participant safety, the design and conduct of the study, or the study data analysis.

Overall Rationale for the Protocol Amendment

As detailed in the Summary of Changes table below, the main overall rationale for updating to protocol Version 6.0 (Amendment 5) is to clarify ambiguity in Exclusion Criterion #6 and remove an incorrect reference to rescue medication (which is not applicable to this study).

Section #(s), Title(s)	Description of Change	Brief Rationale

Cover Page	• The study Clinical Trials Information System (CTIS) number has been added to the protocol cover page.	• To comply with applicable European Union regulatory guidance

5.2, Exclusion Criteria	• Exclusion Criterion #6 has been modified as follows: Has received prior systemic treatment for metastatic NSCLC. Notes: ○ Prior chemotherapy is permitted, provided that it was used for treatment of locoregional NSCLC as a component of curative intent therapy and administration was completed more than 6 months prior to Screening. ○ Participants with a history of radiotherapy ~~for Stage III NSCLC~~ may be eligible (with a required washout period of ≥ 2 weeks before Screening, as detailed in Inclusion Criterion #9 above); however: ▪ ~~Lesions that received radiotherapy are not included in the calculation of RECIST v1.1.~~ ▪ ~~Radiation in the metastatic setting, for any reason, is not permitted.~~ ▪ Concurrent radiotherapy is not permitted. ▪ Prior EGFR-TKI therapy is not permitted.	• To remove ambiguity concerning the permissible participant population for the study

6.7.1, Rescue Medication *(now deleted)*	• This section of the protocol has been removed.	• To correct an administrative error in previous versions of the protocol; no rescue medication is provided for/applicable to this study.

5.1, Inclusion Criteria 10.4, Appendix 4: Hy's Law Definition, Reporting, and Observation Requirements	• References to direct bilirubin have been removed from Inclusion Criterion #6 and the Hy's Law Definition, Reporting, and Observation Requirements appendix.	• To indicate that total bilirubin alone (not total bilirubin in combination with direct bilirubin) is to be used when determining adequate hepatic function during Screening and when evaluating cases indicative of possible hepatocellular injury (Hy's Law).

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, Three-Arm, Open-Label Phase 3b Clinical Trial of Aumolertinib, versus Aumolertinib with Chemotherapy, versus Osimertinib for Patients with Metastatic NSCLC and an EGFR Mutation (TREBLE)

Protocol Number: EQ143-301

Protocol Version: 6.0 (Amendment 5)

Compound: aumolertinib (EQ143)

Brief Title: Aumolertinib with Chemotherapy or Alone Compared with Osimertinib in Patients with Epidermal Growth Factor Receptor-Mutant Non-Small Cell Lung Cancer

Rationale: Whether the addition of chemotherapy to a third-generation epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI), such as aumolertinib, improves progression-free survival (PFS) in patients with metastatic EGFR-mutated non-small cell lung cancer (NSCLC) is unknown. In particular, the efficacy, safety, and tolerability of this approach compared with that of EGFR-TKI monotherapy in patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 has not been studied prospectively.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy of aumolertinib in combination with chemotherapy compared with osimertinib monotherapy	• PFS, as assessed by blinded independent central review (BICR) per RECIST v1.1
Key Secondary	
• To further assess the efficacy of aumolertinib in combination with chemotherapy compared with osimertinib monotherapy	• OS
Other Secondary	
• To assess other efficacy measures of aumolertinib in combination with chemotherapy compared with osimertinib monotherapy	• TGR, ORR, DCR, DepOR, and DoR, each assessed by BICR per RECIST v1.1 • PFS, TGR, ORR, DCR, DepOR, and DoR, each assessed by the Investigator per RECIST v1.1 • ctDNA clearance

Objectives	Endpoints
• To assess the efficacy of aumolertinib monotherapy compared with osimertinib monotherapy	• PFS, TGR, ORR, DCR, DepOR, and DoR, each assessed by BICR per RECIST v1.1 • PFS, TGR, ORR, DCR, DepOR, and DoR, each assessed by the Investigator per RECIST v1.1 • OS • ctDNA clearance
• To assess safety, including toxicities mediated by EGFR WT inhibition, in the study treatment arms	• TEAEs, vital signs, ECGs, and laboratory test results (including chemistry, hematology, and urinalysis) by treatment arm
• To evaluate selected PROs and QoL, including toxicities mediated by EGFR WT inhibition, in the study population	• NCI PRO-CTCAE questionnaire
• To characterize the PK profile of aumolertinib alone and in combination with chemotherapy	• Aumolertinib concentration for population PK analysis
Exploratory	
• To characterize mechanisms of acquired resistance in the treatment population	• Exploratory biomarker analysis of plasma samples banked for the purpose of characterizing resistance mechanisms in participants treated with aumolertinib in combination with chemotherapy, aumolertinib monotherapy, and osimertinib monotherapy
• To evaluate CNS efficacy for participants in the study treatment arms with measurable CNS lesions at baseline	• Description of CNS efficacy as measured by PFS; OS; and ORR, DCR, DepOR, and DoR (each assessed by the Investigator per Response Assessment in Neuro-Oncology [RANO] criteria)
• To evaluate additional efficacy measures in the study treatment arms	• PFS2, as applicable • TFST and TSST, as applicable
• To evaluate the correlation between TGR and ctDNA clearance with PFS and OS in the study treatment arms	• TGR, ctDNA, PFS assessed by the Investigator per RECIST v1.1, and OS
• To evaluate the exposure-response relationship of aumolertinib alone and in combination with chemotherapy	• Exposure-response analysis of safety and efficacy endpoints

Overall Design:

EQ143-301 (TREBLE) is a Phase 3b, multicenter, randomized, 3-arm, open-label study of aumolertinib + chemotherapy combination therapy compared with osimertinib monotherapy, and aumolertinib monotherapy described in comparison with osimertinib monotherapy. Approximately 200 study sites in multiple regions are currently planned to participate.

The primary study endpoint is efficacy by PFS (as assessed by BICR per RECIST v1.1). PFS is defined as the time from date of participant randomization to either the first date of disease progression (per RECIST v1.1) or the date of death by any cause, whichever occurs first.

Brief Summary:

The purpose of this study is to evaluate the efficacy and safety of aumolertinib alone, aumolertinib with chemotherapy, and osimertinib alone (active comparator) in systemic treatment-naïve participants who have metastatic EGFR-mutant NSCLC and an ECOG PS of 0, 1, or 2.

Additional study details include the following:

- The study duration will be 5 years or more.
- A cycle of treatment is defined as 21 days for all arms.
  - Cycles 2 onward have a window of 2 days prior to, or 7 days following, the cycle due date.
- Participants can continue to receive study treatment as long as they have not withdrawn consent and are judged by the Investigator to continue to receive clinical benefit, in the absence of meeting other treatment and/or study discontinuation criteria.

Number of Participants:

Approximately 500 participants will be randomized in a 2:2:1 ratio (by the stratified permuted block randomization method) and enrolled into one of 3 study treatment arms: aumolertinib + chemotherapy combination therapy, osimertinib monotherapy, or aumolertinib monotherapy, respectively.

Note: "Enrolled" in the context of the clinical study means the agreement of a participant to participate in the study following completion of the informed consent process. Potential participants who are screened for the purpose of determining study eligibility, but are not randomized to study treatment (ie, are not eligible for study participation), are not considered enrolled.

Intervention Groups and Duration:

Approximately 500 study participants will be randomized in a 2:2:1 ratio (by stratified permuted block randomization method) and enrolled into one of 3 study treatment arms:

1. **Aumolertinib with chemotherapy** (platinum-based doublet), as follows ***(approximately 200 participants)***:
    - For adenocarcinoma, either:
        - Aumolertinib + cisplatin with pemetrexed, **or**
        - Aumolertinib + carboplatin with pemetrexed
    - For squamous cell carcinoma, one of the following:
        - Aumolertinib + cisplatin or carboplatin with paclitaxel;
        - Aumolertinib + cisplatin or carboplatin with albumin-bound paclitaxel; **or**
        - Aumolertinib + cisplatin or carboplatin with gemcitabine
2. **Osimertinib alone *(approximately 200 participants)***
3. **Aumolertinib alone *(approximately 100 participants)***

All participants will be stratified by the following factors:

- EGFR mutation (ex19del versus L858R)
- ECOG PS (0 versus 1/2)
- Race (White versus Asian versus Other Races Combined)

Aumolertinib will be administered as two 55-mg tablets for a total dose of 110 mg once daily. Each aumolertinib tablet contains EQ143 drug substance, microcrystalline cellulose (KG802), anhydrous lactose (21AN), sodium carboxymethyl starch (type A), sodium stearyl fumarate, and magnesium stearate (MF-2-V). Based on current available data, aumolertinib may be taken with or without food.

Osimertinib will be administered as a single 80-mg tablet once daily.

While selected participants with a percutaneous endoscopic gastrostomy (PEG) tube may be eligible for this study at Investigator discretion, aumolertinib and osimertinib tablets are not to be crushed or otherwise damaged.

Participants randomized to receive aumolertinib with chemotherapy will receive up to 4 cycles of a platinum-based doublet, along with once-daily aumolertinib at 110 mg.

Thereafter, at the Investigator's discretion as based on assessment of continued clinical benefit, the participant may go on to receive maintenance pemetrexed with once-daily aumolertinib for the remainder of their time on study treatment—provided that they do not meet any of the study treatment discontinuation and/or overall study discontinuation criteria.

As specified in the SoAs (Section 1.3), participants will continue on study treatment until disease progression (with certain exceptions, as noted immediately below), withdrawal of consent, Investigator decision, or other reasons as detailed in Section 7.2.

Note: Based upon Investigator judgment, selected participants who experience confirmed disease progression (per RECIST v1.1) may be permitted to continue post-progression study treatment upon discussion with and approval by the Sponsor. These participants, who will be required to sign a separate ICF, must meet **both** of the following criteria to continue their assigned study treatment after progression:

- No decline in ECOG PS attributable to underlying disease.
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression).

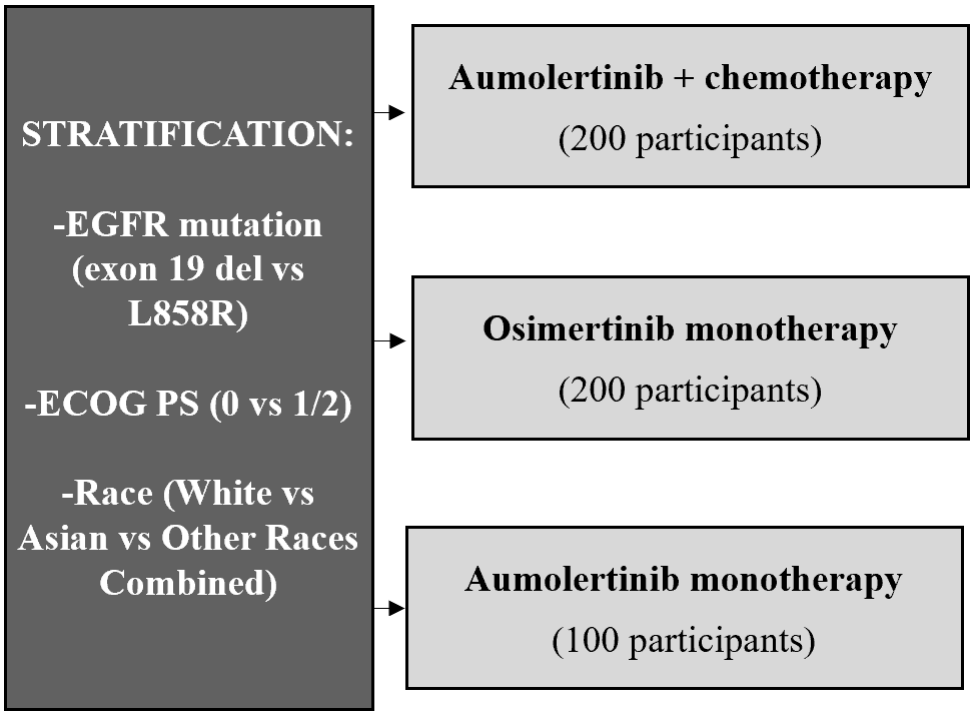
Committee for Blinded Independent Central Review:

A central blinded Independent Review Committee will be used for the primary study endpoint of BICR-assessed PFS (per RECIST v1.1). BICR will also be used to evaluate images collected during the study for assessment of the secondary tumor-based efficacy endpoints.

A separate charter will define the procedures used by this committee for the purposes of BICR.

1.2. Schema

Figure 1: Study Schema (EQ143-301 [TREBLE])



del = deletion; EGFR = epidermal growth factor receptor; ECOG PS = Eastern Cooperative Oncology Group performance status.

1.3. Schedules of Activities (SoAs)

The study SoAs are presented by treatment arm, as follows: the aumolertinib monotherapy arm in Table 1; the aumolertinib with chemotherapy arm in Table 2; and the osimertinib monotherapy arm in Table 3.

Table 1: Aumolertinib Monotherapy Arm – SoA (EQ143-301 [TREBLE])

Study Period:	**Screening[a]**		**Study Treatment[a, h] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up [k, n]**	**Survival Follow-up[l]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treatment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
General Screening Procedures												
Study Informed Consent	X											
IRT Screening (after ICF Signature)	X											
Participant History & Study Eligibility Review												
Demographics/Baseline Characteristics	X											
Inclusion/Exclusion Criteria	X											
Medical History & Current Medical Conditions	X											
Prior & Concomitant Medications/Procedures Review	X		X	X	X	X	X	X	X			
Smoking Status	X											
SARS-CoV-2 Vaccination, Symptom, & Testing Review[j]	X											
Diagnosis & Extent of Cancer	X											
Prior Anticancer Therapy	X											
IRT – Randomization		X										

Study Period:	**Screening[a]**		**Study Treatment[a, h] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up [k, n]**	**Survival Follow-up[l]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treat-ment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
IRT – Study Drug Dispensation (Participant Dispensation)			X	X	X	X	X	X	X			
ECOG PS & Physical Examinations												
Physical Exam		X	X[c]	X	X	X	X	X	X			
ECOG PS		X	X[c]	X	X	X	X	X	X			
Height		X										
Body Weight		X	X[c]	X	X	X	X	X	X			
Vital Signs		X	X[c]	X	X	X	X	X	X			
Laboratory Assessments*,[o]												
EGFR Mutation Testing[p]	X (pre-screening)[p]		X									
Hematology: ANC[o], Hgb, WBC, & PLAT		X	X[c]	X	X	X	X	X	X			
Hematology: all other labs listed in Section 10.8.1			As clinically indicated									
Serum Chemistry: ALT, ALP, AST, TBIL + IBILI, CPK, calculated CLCr[o], CREAT[o], & GLU[o]		X	X[c]	X	X	X	X	X	X			
Serum Chemistry: all other labs listed in Section 10.8.2			As clinically indicated									
Coagulation: PT/INR		X	As clinically indicated									

Study Period:	**Screening[a]**		**Study Treatment[a, h] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up [k, n]**	**Survival Follow-up[l]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treatment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
Urinalysis: dipstick parameters (refer to Section 10.8.3)			As clinically indicated									
Pregnancy Test (all female participants of childbearing potential)[d]		X (≤ 48 h pre-first dose)										
Pregnancy Test (only female participants of childbearing potential who are not on contraception[d])			X	X	X	X	X	X	X			
Blood Sample Collection for ctDNA Analysis[m]			X[m]	X	X	At disease progression (as appl.)						
Cardiac Assessments												
ECG[e]		X	X[c]			X						
ECHO or MUGA (LVEF)[g]	X		X[c]			X[g]						
Pharmacokinetic Assessments												
PK Blood Sample Collection[f]			X	X	X	X	X					

Study Period:	**Screening[a]**		**Study Treatment[a, h] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up [k, n]**	**Survival Follow-up[l]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treat-ment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
Other Safety Assessments												
AE/SAE Collection	Continuous										Refer to footnote "k"	Refer to footnote "l"
SARS-CoV-2 Testing (per institutional standards & local/country regulations)[j]	As appl.											
Tumor Assessments												
CT of Chest & Abdomen/Pelvis with Contrast (or PET/CT, at Inv. discretion)[h]	X		q6wk (± 3 days) for first 3 post-baseline assessments, then q12wk[h]									
Brain Imaging for Participants with Baseline Brain Metastases[i]	X		q6wk (± 3 days) for first 3 post-baseline assessments, then q12wk[h]									
Brain Imaging for Participants without Baseline Brain Metastases	X		If clinically indicated (as appl.)[h,i]									
Archival Tissue Collection for CDx Testing[q] **(only if available; not required)**	X											
Patient-Reported Outcomes & Quality of Life Assessments												
PRO/QoL Assessment (NCI PRO-CTCAE)			qwk	qwk	qwk	qwk	X	X	q6wk	X		
IRT – Discontinuation										X		
Follow-up Assessments (Post-Discontinuation of Study Treatment)												

Study Period:	**Screening[a]**		**Study Treatment[a, h] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up [k, n]**	**Survival Follow-up[l]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treat-ment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
Review of Any Anticancer Therapies since Study Treatment D/C (as appl.)												X
AE/SAE Collection[k]											X	
Treatment-Related SAE Collection[l]												X
Survival Status[l]												X

***** Laboratory assessments are to be conducted predose, and processed by local laboratory, unless otherwise specified in the protocol. Clinical safety labs for screening and enrollment purposes will be processed using a licensed laboratory/laboratory with applicable local accreditation.

[a] The Investigator is to make every effort to obtain assessments at each time point, including if a participant discontinues from the study. In the context of SARS-CoV-2 or other pandemics, natural disasters, or major disruptions, provisions may be made to accommodate participants who are unable to attend onsite study visits for scheduled assessments and dispensation of study intervention.

[b] Each treatment cycle is 21 days. For Cycles 2 onward, there is a window of -2 days or +7 days from the due date for that cycle.

[c] If C1D1 and Screening are within 7 days of each other, then this assessment does not need to be repeated on C1D1.

[d] Serum or urine Screening pregnancy test is required for all female participants of childbearing potential; this test must be completed within 48 hours before the participant's first dose of any study intervention.

- Female participants of childbearing potential who are not on contraception (and therefore must agree be abstinent to comply with the study requirements; refer to Section 10.3.2) are to have serum or urine pregnancy testing performed during each dosing visit, prior to dosing with any study intervention.
- Additional serum or urine pregnancy testing may be performed at any other time point at Investigator discretion.

[e] ECG schedule (prior to PK sampling): C1D1 – predose (within 30 minutes before dosing) and 2 hours to 6 hours (± 30 minutes) postdose; C4D1 – within 30 minutes before dosing and 2 hours to 6 hours (± 30 minutes) postdose. ECG may also be performed at any other time point as clinically indicated.

[f] PK blood sampling schedule for the aumolertinib monotherapy arm (during participant clinic visits for clinical assessment): PK samples should be collected prior to the study drug dose (within 30 minutes before dosing) on C2D1, C3D1, C4D1, and C5D1. PK samples should be collected post-study drug dose (between 2 hours and 8 hours [± 30 minutes] after dosing) on C1D1 and C2D1.

[g] Whenever possible, the same imaging modality (ECHO or MUGA) should be used across all LVEF collections for the individual participant. Screening imaging results must be provided prior to the first dose on C1D1 (ie, baseline).

[h] Note that all tumor imaging assessments, including brain imaging assessments (refer to footnote "i"), are to be performed at the scheduled interval of q6wk (± 3 days) for the first 3 post-baseline assessments (with "baseline" defined as the participant's most recent scan performed prior to the first dose of any study intervention and within 28 days before C1D1), then q12wk thereafter, regardless of whether the participant's treatment cycle is delayed.

- For all participants, CT scans of the chest and abdomen/pelvis with contrast (or PET/CT, at Investigator discretion) are to be collected at baseline.
- The same imaging modality should be used across all tumor assessment scan collections for the individual participant.
- Whenever possible, any participant who discontinues from study treatment for a reason other than disease progression should have CT with contrast (or PET/CT, as applicable) performed if they have not undergone a scan within the prior 4 weeks.

[i] Brain imaging in this study is to be performed as clinically indicated. General guidance, which may be modified for an individual participant at Investigator discretion, is as follows:

- For participants with baseline brain metastases: In general, brain imaging every 3 months is recommended per RANO criteria (Chukwueke 2019).
  - For participant and Investigator/site convenience in this study, RANO-based assessments are scheduled to occur in parallel with RECIST v1.1-based assessments (q6wk [± 3 days] for the first 3 post-baseline assessments and q12wk thereafter).
  - All brain imaging assessments are to be performed at the scheduled interval, regardless of whether the participant's treatment cycle is delayed.
  - MRI is the preferred modality for brain imaging; CT may be used if MRI is medically contraindicated. Whenever possible, the same modality should be used across all brain imaging collections for the individual participant.
- For participants without baseline brain metastases: No prescheduled follow-up brain imaging is required.

[j] There are no protocol-specified testing requirements for SARS-CoV-2 in this study. SARS-CoV-2 requirements are instead determined by institutional standards (and local/country regulations, as applicable) and Investigator judgment.

- At Investigator discretion, any participant who tests positive and/or is symptomatic for SARS-CoV-2 during Screening may either be excluded from the study or delay enrollment until active infection has been excluded per institutional standards.
- During the study, any SARS-CoV-2 testing is to be performed as clinically indicated for the individual participant. The Investigator must document the results of all tests performed. Any confirmed infection is to be recorded as an AE or, in the event that clinical manifestation warrants such, recorded and handled as an SAE as detailed in Section 10.2.4.

[k] All participants who discontinue study treatment, but do not withdraw overall consent, will remain in the study for safety follow-up. Safety follow-up will begin at the time of the participant's discontinuation from study treatment and continue through 28 days after their last dose of any study intervention, or until the start of a new anticancer therapy (whichever occurs first).

- AEs and SAEs are recorded from time of informed consent throughout the safety follow-up period. All AEs and SAEs occurring during this period are to be reported and handled as detailed in Section 10.2.4.
- The Safety Follow-up Visit can be conducted virtually.

[l] For all participants who have discontinued study treatment, but have not withdrawn overall consent, survival follow-up is to be performed approximately every 12 weeks after their last dose of any study intervention until the participant's death or the end of the overall study (whichever occurs first).

- At approximately q12wk intervals, good effort (defined as at least 3 attempts) should be made by the Investigator or designee to follow up with the participant or caregiver, either by telephone or secure electronic communication.
- The Investigator or designee should obtain any available information on known aspects of the participant's status, including survival status and (as applicable) any subsequent initiation of anticancer therapy and any SAEs considered treatment-related by the Investigator.

[m] Blood samples for ctDNA analysis are to be collected predose (within 30 minutes before dosing) on Day 1. However, in the event that the Day 1 sample is obtained after dosing, that sample should not be discarded, but instead included for analysis with appropriate annotation as to sample time relative to time of active treatment administration. All other samples for ctDNA analysis may be collected before, during, or after dosing. All ctDNA samples will be processed by central laboratory.

[n] For participants who discontinue study treatment without experiencing disease progression, but do not withdraw overall consent, tumor assessments will continue until confirmed progression (per RECIST v1.1); initiation of subsequent anticancer therapy; or withdrawal from the study.

[o] For participants in the aumolertinib monotherapy arm, ANC, calculated CLCr, and CREAT are required at Screening only, and then only as clinically indicated. GLU is to be collected in the fasted state at Screening and non-fasted at all other time points.

[p] For screening and enrollment purposes, all participants are to have undergone EGFR mutation testing (of blood or tissue) performed by clinically validated assay, using a licensed laboratory/laboratory with applicable local accreditation.

- If available, existing EGFR mutation test results may be used to confirm participant eligibility, provided that they were obtained within ≤ 3 months prior to study entry.
- The Investigator may recommend that prospective participants for whom EGFR mutation testing is not covered or reimbursed by standard of care undergo pre-screening confirmatory testing. Any such individual will be required to sign a Pre- Screening ICF allowing blood or tissue sample collection for local EGFR mutation testing prior to the 28-day study Screening window. Refer to Appendix 9 (Section 10.9) for details.
- For all participants in the study, blood will also be collected at C1D1 for central retrospective testing.

[q] If archival tumor tissue (FFPE or unstained slides) is available (regardless of when it was obtained), it should also be collected (with participant's consent) for central retrospective testing; however, this is not mandatory.

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; appl. = applicable; approx. = approximately; AST = aspartate aminotransferase; C = study Cycle; CDx = companion diagnostic; CLCr = creatinine clearance; CPK = creatine phosphokinase; CREAT = creatinine; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating tumor deoxyribonucleic acid; D = study Day; D/C = discontinuation; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; FFPE = formalin-fixed paraffin-embedded; GLU = glucose; h = hours; Hgb = hemoglobin; IBILI = indirect bilirubin; ICF = informed consent form; INR = International Normalized Ratio; Inv. = Investigator; IRT = interactive response technology; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NCI = National Cancer Institute; PET = positron emission tomography; PK = pharmacokinetic(s); PLAT = platelets; PRO = patient-reported outcome; PT = prothrombin time; QoL = quality of life; qwk = once weekly; q6wk = once every 6 weeks; q12wk = once every 12 weeks; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria for Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TBIL = total bilirubin; WBC = white blood cell.

Table 2: Aumolertinib with Chemotherapy Arm – SoA (EQ143-301 [TREBLE])

Study Period:	**Screening[a]**		**Study Treatment[**, a, h] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up[k, n]**	**Survival Follow-up[l]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treatment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
General Screening Procedures												
Study Informed Consent	X											
IRT Screening (after ICF Signature)	X											
Participant History & Study Eligibility Review												
Demographics/Baseline Characteristics	X											
Inclusion/Exclusion Criteria	X											
Medical History & Current Medical Conditions	X											
Prior & Concomitant Medications/ Procedures Review	X		X	X	X	X	X	X	X			
Smoking Status	X											
SARS-CoV-2 Vaccination, Symptom, & Testing Review[j]	X											
Diagnosis & Extent of Cancer	X											
Prior Anticancer Therapy	X											
IRT – Randomization		X										
IRT – Study Drug** Dispensation (Participant Dispensation)			X	X	X	X	X	X	X			

Study Period:	**Screening[a]**		**Study Treatment[**, a, h] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up[k, n]**	**Survival Follow-up[l]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treatment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
ECOG PS & Physical Examinations												
Physical Exam		X	X[c]	X	X	X	X	X	X			
ECOG PS		X	X[c]	X	X	X	X	X	X			
Height		X										
Body Weight		X	X[c]	X	X	X	X	X	X			
Vital Signs		X	X[c]	X	X	X	X	X	X			
Laboratory Assessments*,[o]												
EGFR Mutation Testing[q]	X (pre-screening)[q]		X									
Hematology: ANC, Hgb, WBC, & PLAT		X	X[c]	X	X	X	X	X	X			
Hematology: all other labs listed in Section 10.8.1			As clinically indicated									
Serum Chemistry: ALT, ALP, AST, TBIL + IBILI, CPK, calculated CLCr[p], CREAT, & GLU[p]		X	X[c]	X	X	X	X	X	X			
Serum Chemistry: all other labs listed in Section 10.8.2			As clinically indicated									
Coagulation: PT/INR		X	As clinically indicated									
Urinalysis: dipstick parameters (refer to Section 10.8.3)			As clinically indicated									
Pregnancy Test (all female participants of childbearing potential)[d]		X (≤ 48 h pre-first dose)										
Pregnancy Test (only female participants of childbearing potential who are not on contraception)[d]			X	X	X	X	X	X	X			

Study Period:	**Screening[a]**		**Study Treatment[**, a, h] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up[k, n]**	**Survival Follow-up[l]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treatment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
Blood Sample Collection for ctDNA Analysis[m]			X[m]	X	X	At disease progression (as appl.)						
Cardiac Assessments												
ECG[e]		X	X[c]			X						
ECHO or MUGA (LVEF)[g]	X		X[c]			X[g]						
Pharmacokinetic Assessments												
PK Blood Sample Collection[f]			X	X	X	X	X					
Other Safety Assessments												
AE/SAE Collection	Continuous										Refer to footnote "k"	Refer to footnote "l"
SARS-CoV-2 Testing (per institutional standards & local/country regulations)[j]	As appl.											
Tumor Assessments												
CT of Chest & Abdomen/Pelvis with Contrast (or PET/CT, at Inv. discretion)[h]	X		q6wk (± 3 days) for first 3 post-baseline assessments, then q12wk[h]									
Brain Imaging for Participants with Baseline Brain Metastases[i]	X		q6wk (± 3 days) for first 3 post-baseline assessments, then q12wk[h]									
Brain Imaging for Participants without Baseline Brain Metastases	X		If clinically indicated (as appl.)[h,i]									
Archival Tissue Collection for CDx Testing[r] **(only if available; not required)**	X											
Patient-Reported Outcomes & Quality of Life Assessments												
PRO/QoL Assessment (NCI PRO-CTCAE)			qwk	qwk	qwk	qwk	X	X	q6wk	X		
IRT – Discontinuation										X		
Follow-up Assessments (Post-Discontinuation of Study Treatment)												

Study Period:	**Screening[a]**		**Study Treatment[**, a, h] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up[k, n]**	**Survival Follow-up[l]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treatment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
Review of Any Anticancer Therapies since Study Treatment D/C (as appl.)												X
AE/SAE Collection[k]											X	
Treatment-Related SAE Collection[l]												X
Survival Status[l]												X

* Laboratory assessments are to be conducted predose, and processed by local laboratory, unless otherwise specified in the protocol. Clinical safety labs for screening and enrollment purposes will be processed using a licensed laboratory/laboratory with applicable local accreditation.

** Participants in the aumolertinib with chemotherapy arm will receive up to 4 cycles of a platinum-based doublet along with once-daily aumolertinib at 110 mg QD. Thereafter, at the Investigator's discretion (based on assessment of continued clinical benefit), the participant may go on to receive maintenance pemetrexed with QD aumolertinib for the remainder of their study treatment—provided that they do not meet study treatment and/or overall study discontinuation criteria. No delay in aumolertinib dosing is necessitated by a delay in chemotherapy dosing (refer to Section 6.5.2).

[a] The Investigator is to make every effort to obtain assessments at each time point, including if a participant discontinues from the study. In the context of SARS-CoV-2 or other pandemics, natural disasters, or major disruptions, provisions may be made to accommodate participants who are unable to attend onsite study visits for scheduled assessments and dispensation of study intervention.

[b] Each treatment cycle is 21 days. For Cycles 2 onward, there is a window of -2 days or +7 days from the due date for that cycle.

[c] If C1D1 and Screening are within 7 days of each other, then this assessment does not need to be repeated on C1D1.

[d] Serum or urine Screening pregnancy test is required for all female participants of childbearing potential; this test must be completed within 48 hours before the participant's first dose of any study intervention.

- Female participants of childbearing potential who are not on contraception (and therefore must agree be abstinent to comply with the study requirements; refer to Section 10.3.2) are to have serum or urine pregnancy testing performed during each dosing visit, prior to dosing with any study intervention.
- Additional serum or urine pregnancy testing may be performed at any other time point at Investigator discretion.

[e] ECG schedule (prior to PK sampling): C1D1 – predose (within 30 minutes before dosing) and 2 hours to 6 hours (± 30 minutes) postdose; C4D1 – within 30 minutes before dosing and 2 hours to 6 hours (± 30 minutes) postdose. ECG may also be performed at any other time point as clinically indicated.

[f] PK blood sampling schedule for the aumolertinib with chemotherapy arm (during participant clinic visits for clinical assessment): PK samples should be collected prior to the study drug dose (within 30 minutes before dosing) on C2D1, C3D1, C4D1, and C5D1. PK samples should be collected post-study drug dose (between 2 hours and 8 hours [± 30 minutes] after dosing) on C1D1 and C2D1.

[g] Whenever possible, the same imaging modality (ECHO or MUGA) should be used across all LVEF collections for the individual participant. Screening imaging results must beprovided prior to the first dose on C1D1 (ie, baseline).

[h] Note that all tumor imaging assessments, including brain imaging assessments (refer to footnote "i"), are to be performed at the scheduled interval of q6wk (± 3 days) for the first 3 post-baseline assessments (with "baseline" defined as the participant's most recent scan performed prior to the first dose of any study intervention and within 28 days before C1D1), then q12wk thereafter, regardless of whether the participant's treatment cycle is delayed.

- For all participants, CT scans of the chest and abdomen/pelvis with contrast (or PET/CT, at Investigator discretion) are to be collected at baseline.
- The same imaging modality should be used across all tumor assessment scan collections for the individual participant.
- Whenever possible, any participant who discontinues from study treatment for a reason other than disease progression should have a CT with contrast (or PET/CT, as applicable) performed if they have not undergone a scan within the prior 4 weeks.

[i] Brain imaging in this study is to be performed as clinically indicated. General guidance, which may be modified for an individual participant at Investigator discretion, is as follows:

- For participants with baseline brain metastases: In general, brain imaging every 3 months is recommended per RANO criteria (Chukwueke 2019).
  - For participant and Investigator/site convenience in this study, RANO-based assessments are scheduled to occur in parallel with RECIST v1.1-based assessments (q6wk [± 3 days] for the first 3 post-baseline assessments and q12wk thereafter).
  - All brain imaging assessments are to be performed at the scheduled interval, regardless of whether the participant's treatment cycle is delayed.
  - MRI is the preferred modality for brain imaging; CT may be used if MRI is medically contraindicated. Whenever possible, the same modality should be used across all brain imaging collections for the individual participant.
- For participants without baseline brain metastases: No prescheduled follow-up brain imaging is required.

[j] There are no protocol-specified testing requirements for SARS-CoV-2 in this study. SARS-CoV-2 requirements are instead determined by institutional standards (and local/country regulations, as applicable) and Investigator judgment.

- At Investigator discretion, any participant who tests positive and/or is symptomatic for SARS-CoV-2 during Screening may either be excluded from the study or delay enrollment until active infection has been excluded per institutional standards.
- During the study, any SARS-CoV-2 testing is to be performed as clinically indicated for the individual participant. The Investigator must document the results of all tests performed. Any confirmed infection is to be recorded as an AE or, in the event that clinical manifestation warrants such, recorded and handled as an SAE as detailed in Section 10.2.4.

[k] All participants who discontinue study treatment, but do not withdraw overall consent, will remain in the study for safety follow-up. Safety follow-up will begin at the time of the participant's discontinuation from study treatment and continue through 28 days after their last dose of any study intervention, or until the start of a new anticancer therapy (whichever occurs first).

- AEs and SAEs are recorded from time of informed consent throughout the safety follow-up period. All AEs and SAEs occurring during this period are to be reported and handled as detailed in Section 10.2.4.
- The Safety Follow-up Visit can be conducted virtually.

[l] For all participants who have discontinued study treatment, but have not withdrawn overall consent, survival follow-up is to be performed approximately every 12 weeks after their last dose of any study intervention, until the participant's death or the end of the overall study (whichever occurs first).

- At approximately q12wk intervals, good effort (defined as at least 3 attempts) should be made by the Investigator or designee to follow up with the participant or caregiver, either by telephone or secure electronic communication.
- The Investigator or designee should obtain any available information on known aspects of the participant's status, including survival status and (as applicable) any subsequent initiation of anticancer therapy and any SAEs considered treatment-related by the Investigator.

[m] Blood samples for ctDNA analysis are to be collected predose (within 30 minutes before dosing) on Day 1. However, in the event that the Day 1 sample is obtained after dosing, that sample should not be discarded, but instead included for analysis with appropriate annotation as to sample time relative to time of active treatment administration. All other samples for ctDNA analysis may be collected before, during, or after dosing. All ctDNA samples will be processed by central laboratory.

[n] For participants who discontinue study treatment without experiencing disease progression, but do not withdraw overall consent, tumor assessments will continue until confirmed progression (per RECIST v1.1); the initiation of subsequent anticancer therapy; or withdrawal from the study.

[o] For participants in the aumolertinib with chemotherapy arm only, safety laboratory test results are to be obtained and reviewed by the Investigator prior to study drug dosing for as long as the participant is receiving non-maintenance chemotherapy.

[p] For participants in the aumolertinib with chemotherapy arm, calculated CLCr is required at Screening only, and then only as clinically indicated. GLU is to be collected in the fasted state at Screening and non-fasted at all other time points.

[q] For screening and enrollment purposes, all participants are to have undergone EGFR mutation testing (of blood or tissue) performed by clinically validated assay, using a licensed laboratory/laboratory with applicable local accreditation.

- If available, existing EGFR mutation test results may be used to confirm participant eligibility, provided that they were obtained within ≤ 3 months prior to study entry.
- The Investigator may recommend that prospective participants for whom EGFR mutation testing is not covered or reimbursed by standard of care undergo pre-screening confirmatory testing. Any such individual will be required to sign a Pre- Screening ICF allowing blood or tissue sample collection for local EGFR mutation testing prior to the 28-day study Screening window. Refer to Appendix 9 (Section 10.9) for details.
- For all participants in the study, blood will also be collected at C1D1 for central retrospective testing.

[r] If archival tumor tissue (FFPE or unstained slides) is available (regardless of when it was obtained), it should also be collected (with participant's consent) for central retrospective testing; however, this is not mandatory.

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; approx. = approximately; AST = aspartate aminotransferase; C = study Cycle; CDx = companion diagnostic; CLCr = creatinine clearance; CPK = creatine phosphokinase; CREAT = creatinine; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating tumor deoxyribonucleic acid; D = study Day; D/C = discontinuation; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; FFPE = formalin-fixed paraffin-embedded; GLU = glucose; Hgb = hemoglobin; IBILI = indirect bilirubin; ICF = informed consent form; INR = International Normalized Ratio; Inv. = Investigator; IRT = interactive response technology; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NCI = National Cancer Institute; PET = positron emission tomography; PK = pharmacokinetic(s); PLAT = platelets; PRO = patient-reported outcome; PT = prothrombin time; QD = once daily; QoL = quality of life; qwk = once weekly; q6wk = once every 6 weeks; q12wk = once every 12 weeks; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria for Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TBIL = total bilirubin; WBC = white blood cell.

Table 3: Osimertinib Monotherapy Arm – SoA (EQ143-301 [TREBLE])

Study Period:	**Screening[a]**		**Study Treatment[a, g] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up[j, m]**	**Survival Follow-up[k]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treatment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
General Screening Procedures												
Study Informed Consent	X											
IRT Screening (after ICF Signature)	X											
Participant History & Study Eligibility Review												
Demographics/Baseline Characteristics	X											
Inclusion/Exclusion Criteria	X											
Medical History & Current Medical Conditions	X											
Prior & Concomitant Medications/ Procedures Review	X		X	X	X	X	X	X	X			
Smoking Status	X											
SARS-CoV-2 Vaccination, Symptom, & Testing Review[i]	X											
Diagnosis & Extent of Cancer	X											
Prior Anticancer Therapy	X											
IRT – Randomization		X										
IRT – Study Drug Dispensation (Participant Dispensation)			X	X	X	X	X	X	X			

Study Period:	**Screening[a]**		**Study Treatment[a, g] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up[j, m]**	**Survival Follow-up[k]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treatment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
ECOG PS & Physical Examinations												
Physical Exam		X	X[c]	X	X	X	X	X	X			
ECOG PS		X	X[c]	X	X	X	X	X	X			
Height		X										
Body Weight		X	X[c]	X	X	X	X	X	X			
Vital Signs		X	X[c]	X	X	X	X	X	X			
Laboratory Assessments*, [m]												
EGFR Mutation Testing[o]	X (pre-screening)[o]		X									
Hematology: ANC[n], Hgb, WBC, & PLAT		X	X[c]	X	X	X	X	X	X			
Hematology: all other labs listed in Section 10.8.1			As clinically indicated									
Serum Chemistry: ALT, ALP, AST, TBIL + IBILI, CPK, calculated CLCr[n], CREAT[n], & GLU[n]		X	X[c]	X	X	X	X	X	X			
Serum Chemistry: all other labs listed in Section 10.8.2			As clinically indicated									
Coagulation: PT/INR		X	As clinically indicated									
Urinalysis: dipstick parameters (refer to Section 10.8.3)			As clinically indicated									
Pregnancy Test (all female participants of childbearing potential)[d]		X (≤ 48 h pre-first dose)	As clinically indicated									

Study Period:	**Screening[a]**		**Study Treatment[a, g] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up[j, m]**	**Survival Follow-up[k]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treatment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
Pregnancy Test (only female participants of childbearing potential who are not on contraception)[d]			X	X	X	X	X	X	X			
Blood Sample Collection for ctDNA Analysis[l]			X[m]	X	X	At disease progression (as appl.)						
Cardiac Assessments												
ECG[e]		X	X[c]			X						
ECHO or MUGA (LVEF)[f]	X		X[c]			X[g]						
Other Safety Assessments												
AE/SAE Collection	Continuous										Refer to footnote "j"	Refer to footnote "k"
SARS-CoV-2 Testing (per institutional standards & local/country regulations)[i]	As appl.											
Tumor Assessments												
CT of Chest & Abdomen/Pelvis with Contrast (or PET/CT, at Inv. discretion)[g]	X	q6wk (± 3 days) for first 3 post-baseline assessments, then q12wk[g]										
Brain Imaging for Participants with Baseline Brain Metastases[h]	X	q6wk (± 3 days) for first 3 post-baseline assessments, then q12wk[g]										
Brain Imaging for Participants without Baseline Brain Metastases	X		If clinically indicated (as appl.)[g]									
Archival Tissue Collection for CDx Testing[p] **(only if available; not required)**	X											

Study Period:	**Screening[a]**		**Study Treatment[a, g] (all treatment cycles = 21 days; from C2 onward, window of -2/+7 days[b])**							**Study Treatment D/C[a]**	**Safety Follow-up[j, m]**	**Survival Follow-up[k]**
Time Point(s):	**D -28 to D -1**	**D -7 to D -1**	**C1 D1**	**C2[b] D1**	**C3[b] D1**	**C4[b] D1**	**C5[b] D1**	**C6[b] D1**	**C7+[b] D1 (non-dosing activities are q12wk)**	**At any point**	**Post-treatment D/C**	**Post-treatment D/C**
Frequency:	**Once**	**Once**								**Once**		
Visit Window for all non-dosing activities:				**± 2 days**							**+ 7 days**	**--**
Patient-Reported Outcomes & Quality of Life Assessments												
PRO/QoL Assessment (NCI PRO-CTCAE)			qwk	qwk	qwk	qwk	X	X	q6wk	X		
IRT – Discontinuation										X		
Follow-up Assessments (Post-Discontinuation of Study Treatment)												
Review of Any Anticancer Therapies since Study Treatment D/C												X
AE/SAE Collection[j]											X	
Treatment-Related SAE Collection[k]												X
Survival Status[k]												X

***** Laboratory assessments are to be conducted predose. All labs will be processed by local laboratory unless otherwise specified in the protocol. Clinical safety labs for screening and enrollment purposes will be processed using a licensed laboratory/laboratory with applicable local accreditation.

[a] The Investigator is to make every effort to obtain assessments at each time point, including if a participant discontinues from the study. In the context of SARS-CoV-2 or other pandemics, natural disasters, or major disruptions, provisions may be made to accommodate participants who are unable to attend onsite study visits for scheduled assessments and dispensation of study intervention.

[b] Each treatment cycle is 21 days. For Cycles 2 onward, there is a window of -2 days or +7 days from the due date for that cycle.

[c] If C1D1 and Screening are within 7 days of each other, then this assessment does not need to be repeated on C1D1.

[d] Serum or urine Screening pregnancy test is required for all female participants of childbearing potential; this test must be completed within 48 hours before the participant's first dose of any study intervention.

- Female participants of childbearing potential who are not on contraception (and therefore must agree be abstinent to comply with the study requirements; refer to Section 10.3.2) are to have serum or urine pregnancy testing performed during each dosing visit, prior to dosing with any study intervention.
- Additional serum or urine pregnancy testing may be performed at any other time point at Investigator discretion.

[e] ECG schedule: C1D1 – predose (within 30 minutes before dosing) and 2 hours to 6 hours (± 30 minutes) postdose; C4D1 – within 30 minutes before dosing and 2 hours to 6 hours (± 30 minutes) postdose. ECG may also be performed at any other time point as clinically indicated.

[f] Whenever possible, the same imaging modality (ECHO or MUGA) should be used across all LVEF collections for the individual participant. Screening imaging results must be provided prior to the first dose on C1D1 (ie, baseline).

[g] Note that all tumor imaging assessments, including brain imaging assessments (refer to footnote "h"), are to be performed at the scheduled interval of q6wk (± 3 days) for the first 3 post-baseline visits (with "baseline" defined as the participant's most recent scan performed prior to the first dose of any study intervention and within 28 days before C1D1), then q12wk thereafter, regardless of whether the participant's treatment cycle is delayed.

- For all participants, CT scans of the chest and abdomen/pelvis with contrast (or PET/CT, at Investigator discretion) are to be collected at baseline.
- The same imaging modality should be used across all tumor assessment scan collections for the individual participant.
- Whenever possible, any participant who discontinues from study treatment for a reason other than disease progression should have a CT with contrast (or PET/CT, as applicable) performed if they have not undergone a scan within the prior 4 weeks.

[h] Brain imaging in this study is to be performed as clinically indicated. General guidance, which may be modified for an individual participant at Investigator discretion, is as follows:

- For participants with baseline brain metastases: In general, brain imaging every 3 months is recommended per RANO criteria (Chukwueke 2019).
  - For participant and Investigator/site convenience in this study, RANO-based assessments are scheduled to occur in parallel with RECIST v1.1-based assessments (every 6 weeks ± 3 days for the first 3 post-baseline assessments and then every 12 weeks thereafter).
  - All brain imaging assessments are to be performed at the scheduled interval, regardless of whether the participant's treatment cycle is delayed.
  - MRI is the preferred modality for brain imaging; CT may be used if MRI is medically contraindicated. Whenever possible, the same modality should be used across all brain imaging collections for the individual participant.
- For participants without baseline brain metastases: No prescheduled follow-up brain imaging is required.

[i] There are no protocol-specified testing requirements for SARS-CoV-2 in this study. SARS-CoV-2 requirements are instead determined by institutional standards (and local/country regulations, as applicable) and Investigator judgment.

- At Investigator discretion, any participant who tests positive and/or is symptomatic for SARS-CoV-2 during Screening may either be excluded from the study or delay enrollment until active infection has been excluded per institutional standards.
- During the study, any SARS-CoV-2 testing is to be performed as clinically indicated for the individual participant. The Investigator must document the results of all tests performed. Any confirmed infection is to be recorded as an AE or, in the event that clinical manifestation warrants such, recorded and handled as an SAE as detailed in Section 10.2.4.

[j] All participants who discontinue study treatment, but do not withdraw overall consent, will remain in the study for safety follow-up. Safety follow-up will begin at the time of the participant's discontinuation from study treatment and continue through 28 days after their last dose of any study intervention or until the start of a new anticancer therapy (whichever occurs first).

- AEs and SAEs are recorded from time of informed consent throughout the safety follow-up period. All AEs and SAEs occurring during this period are to be reported and handled as detailed in Section 10.2.4.
- The Safety Follow-up Visit can be conducted virtually.

[k] For all participants who have discontinued study treatment, but have not withdrawn overall consent, survival follow-up is to be performed approximately every 12 weeks after their last dose of any study intervention until the participant's death or the end of the overall study (whichever occurs first).

- At approximately q12wk intervals, good effort (defined as at least 3 attempts) should be made by the Investigator or designee to follow up with the participant or caregiver, either by telephone or secure electronic communication.
- The Investigator or designee should obtain any available information on known aspects of the participant's status, including survival status and (as applicable) any subsequent initiation of anticancer therapy and any SAEs considered treatment-related by the Investigator.

[l] Blood samples for ctDNA analysis are to be collected predose (within 30 minutes before dosing) on Day 1. However, in the event that the Day 1 sample is obtained after dosing, that sample should not be discarded, but instead included for analysis with appropriate annotation as to sample time relative to time of active treatment administration. All other samples for ctDNA analysis may be collected before, during, or after dosing. All ctDNA samples will be processed by central laboratory.

[m] For participants who discontinue study treatment without experiencing disease progression, but do not withdraw overall consent, tumor assessments will continue until confirmed progression (per RECIST v1.1); the initiation of subsequent anticancer therapy; or withdrawal from the study.

[n] For participants in the osimertinib monotherapy arm, ANC, calculated CLCr, and CREAT are required at Screening only, and then only as clinically indicated. GLU is to be collected in the fasted state at Screening and non-fasted at all other time points.

[o] For screening and enrollment purposes, all participants are to have undergone EGFR mutation testing (of blood or tissue) performed by clinically validated assay, using a licensed laboratory/laboratory with applicable local accreditation.

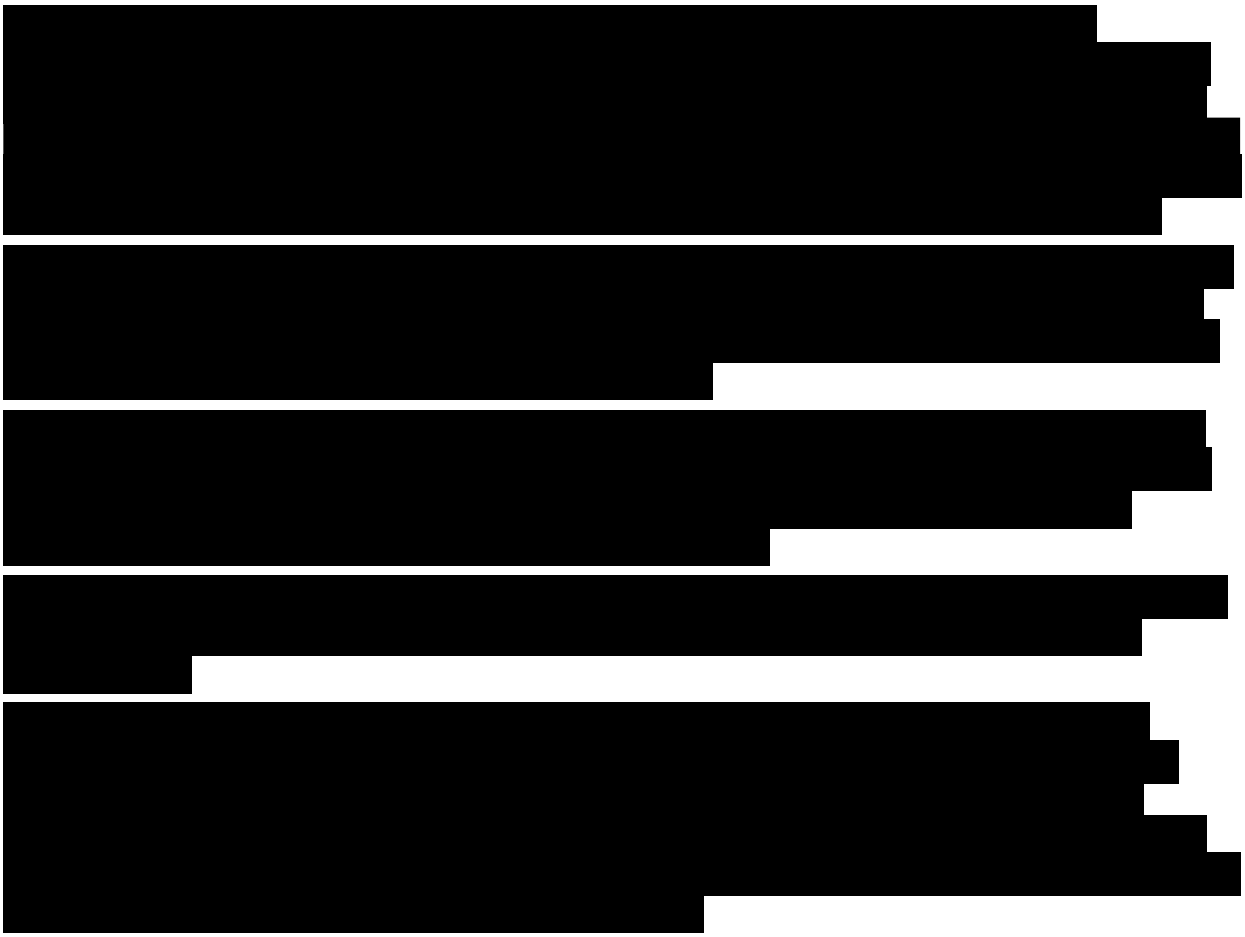
- If available, existing EGFR mutation test results may be used to confirm participant eligibility, provided that they were obtained within ≤ 3 months prior to study entry.
- The Investigator may recommend that prospective participants for whom EGFR mutation testing is not covered or reimbursed by standard of care undergo pre-screening confirmatory testing. Any such individual will be required to sign a Pre- Screening ICF allowing blood or tissue sample collection for local EGFR mutation testing prior to the 28-day study Screening window. Refer to Appendix 9 (Section 10.9) for details.
- For all participants in the study, blood is also to be collected at C1D1 for central retrospective testing.

[p] If archival tumor tissue (FFPE or unstained slides) is available (regardless of when it was obtained), it should also be collected (with participant's consent) for central retrospective testing; however, this is not mandatory.

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; approx. = approximately; AST = aspartate aminotransferase; C = study Cycle; CDx = companion diagnostic; CLCr = creatinine clearance; CPK = creatine phosphokinase; CREAT = creatinine; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ctDNA = circulating tumor deoxyribonucleic acid; D = study Day; D/C = discontinuation; ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; FFPE = formalin-fixed paraffin-embedded; GLU = glucose; Hgb = hemoglobin; IBILI = indirect bilirubin; ICF = informed consent form; INR = International Normalized Ratio; Inv. = Investigator; IRT = interactive response technology; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NCI = National Cancer Institute; PET = positron emission tomography; PLAT = platelets; PRO = patient-reported outcome; PT = prothrombin time; QoL = quality of life; qwk = once weekly; q6wk = once every 6 weeks; q12wk = once every 12 weeks; RANO = Response Assessment in Neuro-Oncology; RECIST = Response Evaluation Criteria for Solid Tumors; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TBIL = total bilirubin; WBC = white blood cell.

2. INTRODUCTION

Aumolertinib (also known as EQ143, HS-10296, HSE-10296, almonertinib, or Ameile™ in China) is a novel, irreversible, small-molecule third generation EGFR inhibitor that is in clinical development for the treatment of patients with EGFR-mutant metastatic NSCLC. It was approved in China in 2020 for the treatment of adult patients with locally advanced EGFR T790M mutation-positive or metastatic NSCLC who have progressed during or after EGFR-TKI therapy. In 2021, the China National Medical Products Administration (NMPA) also approved aumolertinib for the treatment of patients with EGFR exon 19 del or L858R-mutant NSCLC in the first-line setting.



2.1. Study Rationale

The primary purpose of the EQ143-301 (TREBLE) study is to investigate whether the addition of chemotherapy to the third-generation EGFR-TKI aumolertinib improves PFS, as compared with osimertinib monotherapy, in patients with metastatic EGFR-mutated NSCLC.

Overall, the study is designed to:

- Combine key elements of a prospective randomized trial comparing aumolertinib + chemotherapy combination therapy with osimertinib monotherapy, and describing aumolertinib monotherapy in comparison to osimertinib monotherapy

- Compare efficacy and safety measures of aumolertinib and osimertinib within a diverse and inclusive patient population
- Evaluate EGFR WT-mediated toxicity in participants receiving aumolertinib monotherapy, aumolertinib with chemotherapy, or osimertinib monotherapy
- Assess TGR and the clearance of ctDNA with aumolertinib monotherapy, aumolertinib with chemotherapy, and osimertinib monotherapy
- Characterize the PK of aumolertinib in the first-line advanced/metastatic EGFR-mutant setting

2.2. Background

Lung cancer accounts for approximately 11% of all cancers diagnosed globally (Globocan 2020), and NSCLC is the most common type of lung cancer, accounting for approximately 85% of all lung cancer cases. The prognosis remains poor, especially in patients with advanced NSCLC, for whom the median overall survival is only 1 year and the 5-year survival rate is 3.5% (Zhang 2016).

EGFR is a transmembrane protein with an external ligand-binding receptor domain and an intracellular tyrosine kinase domain. EGFR-TKIs have proven to be effective treatments for advanced EGFR-mutated NSCLC. Therefore, clinical guidelines recommend that patients with advanced NSCLC with EGFR-sensitizing mutations receive first-line treatment with TKIs (Cohen 2004, Cohen 2005).

However, most patients develop acquired resistance to first-generation EGFR-targeting TKIs, and disease progression typically occurs after 9 to 14 months of treatment (Maemondo 2010). On disease progression, a “gatekeeper” mutation, T790M, within EGFR is detected in tumor cells or ctDNA from more than 50% of patients and is the most common mechanism of acquired resistance (Kobayashi 2005).

Second-generation irreversible EGFR-TKIs are effective in EGFR-mutant NSCLC, but do not inhibit T790M at clinically achievable concentrations due to dose-limiting toxicity. Thus, there remains a significant unmet medical need for the development of third-generation EGFR inhibitors that can more selectively target the EGFR T790M mutation, sparing WT EGFR. This has led to the development of third-generation EGFR-TKIs, such as osimertinib and aumolertinib.

Osimertinib is a US Food and Drug Administration (FDA)-approved TKI that is standard of care for patients with advanced/metastatic NSCLC and an EGFR-sensitizing mutation in the US.

Initially developed by Hansoh Pharmaceuticals as HS-10296, aumolertinib is a novel, irreversible, small-molecule, third-generation EGFR inhibitor. In nonclinical studies, aumolertinib displayed potent inhibition of EGFR T790M and notably less inhibitory activity on the WT EGFR than other TKIs.

In March 2020, aumolertinib was approved for use in China for the treatment of adult patients with locally advanced or metastatic NSCLC who have experienced disease progression during or after treatment with EGFR-TKIs in the past and have tested positive for the presence of the confirmed EGFR T790M mutation.

In December 2021, aumolertinib was subsequently approved in China for the treatment of patients with EGFR exon 19 del or L858R-mutant NSCLC in the first-line setting.

[redacted]

2.3. Benefit/Risk Assessment

2.3.1. Benefit Assessment

Aumolertinib can selectively inhibit EGFR-sensitizing mutations and T790M drug-resistance mutations. Additionally, aumolertinib has relatively little inhibitory activity on WT EGFR. Based on these characteristics, aumolertinib given in combination with chemotherapy or alone may enhance PFS and tolerability for patients with NSCLC.

2.3.2. Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs for aumolertinib—including risk management of the same—can be found in the summary of safety provided in the current aumolertinib IB.

Overall, the safety profile of aumolertinib is generally consistent with that of other EGFR-TKIs.

Well-known risks associated with EGFR-TKIs which have been observed during clinical trials with aumolertinib, including in the data from the 2 pivotal clinical studies in NSCLC (HS-10296-12-01 and HS-10296-03-01) and from clinical pharmacology studies, are as follows:

- **Hepatoxicity:** Hepatotoxicity was frequently reported in participants with advanced NSCLC treated with 110 mg of aumolertinib in clinical trials. However, this mostly occurred as Grade 1 or 2 elevations in AST, ALT, and other liver function tests. Fatal hepatotoxicity has not been described for aumolertinib.
- **Elevated blood CPK:** Overall, elevations in blood CPK—a recognized risk with EGFR-TKIs—were commonly reported AEs in clinical trials with aumolertinib; however, rhabdomyolysis has not been reported. The frequencies of musculoskeletal pain, myalgia, muscular weakness, and myositis were generally low.
- **Interstitial lung disease:** ILD, including fatal events, has been reported in participants with NSCLC treated with aumolertinib 110 mg in clinical trials.
- **Cardiac failure:** Cardiac failure, including fatal events and events of decreased ejection fraction, has been reported in aumolertinib clinical trials.
- **QTc prolongation:** QTc prolongation has been reported in aumolertinib clinical trials. Events have been primarily low-grade in severity, and no events of Torsades de Pointes have been reported.
- **Ocular toxicity:** Ocular AEs, including dry eye, eye pain, blurred vision, and conjunctivitis, have been reported in aumolertinib clinical trials. Events have been primarily low-grade in severity.

At present, there are no data on the use of aumolertinib in pregnant female participants, and the possible safety risks to the fetus are currently unknown. Based on its mechanism of action, the use of aumolertinib in pregnant female participants may cause harm to the fetus. It is also unknown whether aumolertinib and/or its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded. There are no clinical data for the effect of aumolertinib on human fertility.

In consideration of the above, female participants of childbearing potential should avoid conceiving while taking aumolertinib. Female and male participants should use highly effective contraceptive measures (as detailed in Section 10.3) during heterosexual intercourse throughout the study and for 12 weeks after completing study treatment.

For information on risks associated with the other study interventions, refer to the current prescribing information for osimertinib, pemetrexed, cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, or gemcitabine, as applicable.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential and identified risks in association with aumolertinib are justified by the anticipated benefits that may be afforded to patients with NSCLC.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the efficacy of aumolertinib in combination with chemotherapy compared with osimertinib monotherapy	• PFS, as assessed by blinded independent central review (BICR) per RECIST v1.1
Key Secondary	
• To further assess the efficacy of aumolertinib in combination with chemotherapy compared with osimertinib monotherapy	• OS
Other Secondary	
• To assess other efficacy measures of aumolertinib in combination with chemotherapy compared with osimertinib monotherapy	• TGR, ORR, DCR, DepOR, and DoR, each assessed by BICR per RECIST v1.1 • PFS, TGR, ORR, DCR, DepOR, and DoR, each assessed by the Investigator per RECIST v1.1 • ctDNA clearance
• To assess the efficacy of aumolertinib monotherapy compared with osimertinib monotherapy	• PFS, TGR, ORR, DCR, DepOR, and DoR, each assessed by BICR per RECIST v1.1 • PFS, TGR, ORR, DCR, DepOR, and DoR, each assessed by Investigator per RECIST v1.1 • OS • ctDNA clearance
• To assess safety, including toxicities mediated by EGFR WT inhibition, in the study treatment arms	• TEAEs, vital signs, ECGs, and laboratory test results (including chemistry, hematology, and urinalysis) by treatment arm
• To evaluate selected PROs and QoL, including toxicities mediated by EGFR WT inhibition, in the study population	• NCI PRO-CTCAE questionnaire
• To characterize the PK profile of aumolertinib alone and in combination with chemotherapy	• Aumolertinib concentration for population PK analysis

Objectives	Endpoints
Exploratory	
• To characterize mechanisms of acquired resistance in the treatment population	• Exploratory biomarker analysis of plasma samples banked for the purpose of characterizing resistance mechanisms in participants treated with aumolertinib in combination with chemotherapy, aumolertinib monotherapy, and osimertinib monotherapy
• To evaluate CNS efficacy for participants in the study treatment arms with measurable CNS lesions at baseline	• Description of CNS efficacy as measured by PFS; OS; and ORR, DCR, DepOR, and DoR (each assessed by the Investigator per RANO criteria)
• To evaluate additional efficacy measures in the study treatment arms	• PFS2, as applicable • TFST and TSST, as applicable
• To evaluate the correlation between TGR and ctDNA clearance with PFS and OS in the study treatment arms	• TGR, ctDNA, PFS assessed by the Investigator per RECIST v1.1, and OS
• To evaluate the exposure-response relationship of aumolertinib alone and in combination with chemotherapy	• Exposure-response analysis of safety and efficacy endpoints

4. STUDY DESIGN

4.1. Overall Design

EQ143-301 (TREBLE) is a Phase 3b multicenter, randomized, 3-arm, open-label study to evaluate aumolertinib + chemotherapy combination therapy compared with osimertinib monotherapy, and to describe aumolertinib monotherapy in comparison with osimertinib monotherapy. The intended study population is systemic treatment-naïve participants with metastatic EGFR-mutant NSCLC. Approximately 200 study sites in multiple regions are currently planned to participate.

The primary study endpoint is efficacy of aumolertinib in combination with chemotherapy compared with osimertinib monotherapy, as measured by PFS (assessed by BICR per RECIST v1.1). PFS is defined as the time from date of participant randomization to either the first date of disease progression (per RECIST v1.1) or the date of death by any cause, whichever occurs first.

Approximately 500 study participants will be randomized in a 2:2:1 ratio (by the stratified permuted block randomization method) into one of the following 3 treatment arms, respectively:

4. **Aumolertinib with chemotherapy** (platinum-based doublet), as follows ***(approximately 200 participants)***:
    - For adenocarcinoma, either:
        - Aumolertinib + cisplatin with pemetrexed, **or**
        - Aumolertinib + carboplatin with pemetrexed
    - For squamous cell carcinoma, one of the following:
        - Aumolertinib + cisplatin or carboplatin with paclitaxel;
        - Aumolertinib + cisplatin or carboplatin with albumin-bound paclitaxel; **or**
        - Aumolertinib + cisplatin or carboplatin with gemcitabine
5. **Osimertinib alone *(approximately 200 participants)***
6. **Aumolertinib alone *(approximately 100 participants)***

All participants will be stratified by the following factors:

- EGFR mutation (ex19del versus L858R)
- ECOG PS (0 versus 1/2)
- Race (White versus Asian versus Other Races Combined)

A cycle of treatment is defined as 21 days for all 3 treatment arms; Cycles 2 onward have a window of 2 days prior to, or 7 days following, the cycle due date.

Note: All tumor imaging assessments are to be performed at the scheduled interval of every 6 weeks (± 3 days) for the first 3 post-baseline assessments (with "baseline" defined as the participant's most recent scan performed prior to the first dose of any study intervention and within 28 days before Day 1 of Cycle 1), then every 12 weeks (refer to the applicable SoA [Section 1.3]). This schedule is to be maintained regardless of any delays in the participant's treatment.

Aumolertinib will be administered in the study as two 55-mg tablets for a total dose of 110 mg once daily. Each aumolertinib tablet contains EQ143 drug substance, microcrystalline cellulose (KG802), anhydrous lactose (21AN), sodium carboxymethyl starch (type A), sodium stearyl fumarate, and magnesium stearate (MF-2-V).

Participants randomized to receive aumolertinib with chemotherapy will receive up to 4 cycles of a platinum-based doublet along with once-daily aumolertinib at 110 mg once daily. Thereafter, at the Investigator's discretion—based on assessment of continued clinical benefit for the individual—the participant may go on to receive maintenance pemetrexed with once-daily aumolertinib for the remainder of their study treatment, provided that they do not meet study treatment discontinuation and/or overall study discontinuation criteria.

Osimertinib will be administered in the study as a single 80-mg tablet once daily.

Based on available data, aumolertinib may be taken with or without food. While participants with a PEG tube may be eligible for this study at Investigator discretion, aumolertinib and osimertinib tablets are not to be crushed or otherwise damaged.

As specified in the applicable SoA (Section 1.3), participants will continue on study treatment until disease progression (with certain exceptions, as noted below), withdrawal of consent, Investigator decision, or other reasons as detailed in Section 7.2.

- **Note:** Selected participants who experience confirmed disease progression (per RECIST v1.1) may—at the discretion of the Principal Investigator—be permitted to continue on therapy upon discussion with the Sponsor. These participants must meet **both** of the criteria listed in Section 7.1 to continue on their assigned study treatment after progression, and will be required to sign a separate ICF.

Refer to the SoAs in Section 1.3 for the list of study assessments and corresponding time points presented by treatment arm. Safety assessments conducted in all treatment arms will include monitoring of AEs/SAEs, vital signs, physical examination findings, ECGs, and laboratory test results (including hematology, serum chemistry, urinalysis, and coagulation).

Participants who discontinue study treatment but do not withdraw overall consent will remain in the study for safety and survival follow-up, as detailed in the applicable SoA (Section 1.3).

Pharmacokinetic (PK) plasma samples will be collected from all participants in the aumolertinib and aumolertinib with chemotherapy treatment arms (not the osimertinib arm), as indicated in the applicable SoAs (Table 1 and Table 2, respectively). These PK samples will be analyzed for the concentrations of aumolertinib and its major metabolite, HAS-719, using a validated bioanalytical method. A population PK assessment will be performed, using nonlinear mixed-effect models.

4.2. Scientific Rationale for Study Design

The primary purpose of the EQ143-301 (TREBLE) study is to investigate whether the addition of chemotherapy to the third-generation EGFR-TKI aumolertinib improves PFS in patients with metastatic EGFR-mutated NSCLC. The rationale for dose selection is further detailed in Section 4.3.

4.2.1. Scientific Rationale for Evaluation of Tumor Growth Rate

TGR, which is derived from radiologic tumor measurements in clinical trials, has been found to correlate with PFS and OS in a number of malignancies. The rate of tumor growth—referred to as "g" (defined as the constant exponential rate of tumor growth)—is another surrogate for PFS that has been investigated in the setting of NSCLC, including in several FDA-authored studies.

Gong 2020 observed that "g" was inversely correlated with survival in 5532 cases of advanced NSCLC, with this finding consistent across lines and types of therapy. More specifically, growth rate after nadir of tumor volume is reached on treatment is correlated with survival for EGFR-mutant NSCLC (Nishino 2021).

The aforementioned findings demonstrate key advantages associated with utilizing TGR as an analysis of efficacy in NSCLC: unlike PFS, which uses data captured in discrete intervals of time, estimates of the rates of tumor growth yield data along a continuum—an output that might be preferential to the participant as an earlier indicator of response.

A detailed TGR analysis plan (Section 9.4.3.3.4) will be included in the study SAP.

4.3. Rationale for Dose Selection

In this study, eligible participants will be randomized 2:2:1 to receive aumolertinib 110 mg once daily in combination with chemotherapy (platinum-based doublet); osimertinib 80 mg once daily as monotherapy; or aumolertinib 110 mg once daily as monotherapy, respectively.

Aumolertinib at the 110 mg once-daily dose was approved by the China NMPA in March 2020 for the treatment of patients with EGFR T790M mutation-positive NSCLC who have progressed during or following treatment with other EGFR-TKIs. In December 2021, the NMPA also approved aumolertinib for the treatment of patients with EGFR exon 19 del or L858R-mutant NSCLC in the first-line setting.

The 110 mg once-daily dose of aumolertinib chosen for evaluation in this study is supported by a combination of safety and efficacy data across the Phase 1, Phase 2, and Phase 3 studies in the aumolertinib clinical development program.

Safety data collected across the Phase 1/2 clinical study in participants with NSCLC (Study HS-10296-12-01, conducted in China) showed a dose-dependent increase in the incidence of ≥ Grade 3 AEs and SAEs. This increase was observed across the dose range evaluated (55 mg to 260 mg). However, the overall frequency of ≥ Grade 3 AEs was low in both the 55-mg and 110-mg dose groups. Aumolertinib administered at a dose of 110 mg once daily was found to be safe and well tolerated, with a safety profile consistent with its mechanism of action.

In the pivotal Phase 2 dose-extension portion of Study HS-10296-12-01, aumolertinib at a dose of 110 mg once daily achieved a high level of efficacy.

Based on the August 2021 data cut, as assessed by Investigator, ORR was 61.9% and the DCR was 91.8%, while median PFS and median DoR were 12.4 months and 13.8 months, respectively.

In the pivotal Phase 3 study in participants with NSCLC (Study HS-10296-03-01, conducted in China), aumolertinib at 110 mg once daily was shown to significantly prolong PFS (median of 19.8 months) and DoR (median of 19.2 months) as assessed by Investigator, compared with gefitinib (median of 9.7 months and 8.3 months for PFS and DoR, respectively).

Aumolertinib was also associated with fewer side effects than gefitinib in the first-line treatment of patients with advanced EGFR-mutated NSCLC (Lu 2021).

Overall, the 110 mg once-daily dosing regimen for aumolertinib has been proposed based on robust clinical experience (safety and efficacy) in Phase 1 through Phase 3 studies conducted in participants who have NSCLC.

The dosing regimens for the other study interventions (ie, osimertinib and chemotherapy) are per current standard of care.

Dose Modifications Upon Adverse Reactions

Aumolertinib dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the participant's aumolertinib dose should be reduced to 55 mg once daily. Dose reduction guidelines for aumolertinib adverse reactions are provided in Section 6.5.

Any dose modifications for the other study interventions are to occur in accordance with the current local label for osimertinib, pemetrexed, cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, or gemcitabine, as applicable, and with institutional standard of care.

4.4. End of Study

The end of the overall study will be reached when all participants have ended their participation in the study.

Additionally, the study may be placed on hold or terminated in any of the following circumstances:

- Overall, country-/region-specific, or site-specific study hold or termination by the Sponsor at any time, for any reason
- Study hold or termination in a specific country/region by the relevant Health Authority
- Study-site closure initiated by the IRB/IEC, or by the Principal Investigator as detailed in Section 10.1.9.3

Refer to Section 7.4 for additional information.

The Sponsor will notify the Investigators in the event of any study hold or termination, or in the event of overall study completion (defined as completion of the last study visit of the last participant in the study).

5. STUDY POPULATION

The EQ143-301 (TREBLE) study population will consist of participants who have not received systemic therapy for recurrent or metastatic EGFR-mutant NSCLC and have an ECOG PS of 0, 1, or 2. All participants must be able to provide signed informed consent, and must meet all of the other study inclusion criteria and none of the study exclusion criteria.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in this study only if **all** of the following criteria apply:

1. Is capable of giving signed informed consent, as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol.
2. Is at least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) and capable of complying with the study procedures.
3. Has pathologically confirmed NSCLC that is Stage IIIB or Stage IIIC (for selected participants who are not candidates for curative approaches per the treating Investigator); metastatic (Stage IVA or IVB); or recurrent, **and** which is not amenable to curative intent therapy.
    - **Note:**
        - Participants with brain metastases may be eligible if they are minimally symptomatic or asymptomatic (as judged by their treating physician); have a minimum life expectancy of 12 weeks; **and** are either not on any steroids or on a stable or tapering dose of steroids.
4. Tumor harbors one of the 2 common EGFR mutations known to be associated with EGFR-TKI sensitivity—ex19del or L858R—either alone or in combination with other EGFR mutations (eg, G719X, exon 20 insertions, S7681, L861Q).
    - **Notes:**
        - For screening and enrollment purposes, EGFR mutation status testing (of collected blood or tissue) is to have been performed by clinically validated assay, using a licensed laboratory/laboratory with applicable local accreditation (refer to Section 8.1.5). If available, existing EGFR mutation test results may be used to confirm eligibility, provided that they were obtained within ≤ 3 months prior to study entry.
        - If available, archival tissue may be collected (with participant's consent) at Screening for central retrospective testing (this is **optional**; refer to Section 8.1.5). There is no specific prior interval during which the archival tissue must have been obtained.
        - All participants will also have a blood sample for central retrospective EGFR mutation testing collected predose on Day 1 of treatment Cycle 1.

5. Has ECOG PS of 0, 1, or 2 at the time of enrollment.
6. Has adequate organ function, as defined by **all** of the following:
   - AST and ALT ≤ 3 × ULN
   - TBIL ≤ 1.5 × ULN in participants with well-documented absence of Gilbert's Syndrome
   - Calculated CLcr ≥ 45 mL/min, as estimated by Cockroft-Gault equation
   - ANC ≥ 1000 cells/mm^3
   - Hgb ≥ 8.0 g/dL
   - International Normalized Ratio (INR) ≤ 1.5, **unless** the participant is receiving chronic anticoagulation therapy as noted below.
     – **Note:** Therapeutic INR is higher in individuals on chronic anticoagulation treatment. Any such participant whose INR exceeds 1.5 may be considered eligible per Investigator judgment if otherwise meeting the study entry criteria.
   - PLAT ≥ 100,000/mm^3
7. Has QTc interval of ≤ 470 ms.
8. Must meet all of the applicable requirements for pregnancy and contraception, as follows:
   a. If female:
      - Is a participant of childbearing potential (as defined in Section 10.3.1) who:
        – Has a negative serum or urine pregnancy test result within 48 hours prior to initiation of study drug dosing;
        – Is not breastfeeding;
        – Agrees to use highly effective contraceptive measures (as defined in Section 10.3.2) during heterosexual intercourse, or—if not using contraception—to remain abstinent (refer to Section 10.3.2) and undergo pregnancy testing predose during each dosing visit, while receiving study treatment (all 3 arms) through 12 weeks following the completion of study treatment; **and**
        – Agrees not to donate ova for the same time period;

        or
      - Is a participant who is confirmed by the Investigator to be of non-childbearing potential or medically postmenopausal per one or more of the following parameters:
        – Age, in addition to any of the other parameters listed here;
        – Menses status (ie, absence of menses for ≥ 1 year); or

  - Surgical status (ie, prior hysterectomy, bilateral salpingectomy, bilateral oophorectomy, or bilateral tubal ligation/occlusion); or
  - FSH level.

b. If male:

- Agrees to use a highly effective method of contraception (eg, male condom in addition to hormonal contraception; refer to Section 10.3) during heterosexual intercourse while receiving study treatment (all 3 arms) through 12 weeks following the completion of study treatment; **and**
- Agrees to refrain from donating sperm for the same time period.

Notes:

- For all study participants, contraceptive use must be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Refer to Section 10.3 for additional guidance.
- All participants must follow the contraception duration requirements for the drugs they receive, in accordance with the current local label for each drug.

9. Must adhere to the following washout period requirements for all protocol-permitted prior anticancer therapies (all periods are in relation to Screening):

- Major surgery: 4 weeks
- Chemotherapy: 6 months
- All other permitted therapies, including permitted radiotherapy (refer to Exclusion Criterion #6 below): 2 weeks

5.2. Exclusion Criteria

Participants are excluded from this study if **any** of the following criteria apply:

Medical Conditions

1. Has refractory nausea and vomiting; chronic gastrointestinal disease(s); inability to swallow the formulated product (or for selected participants, to receive it by PEG tube as noted below); or a history of previous significant bowel resection—any of which would preclude adequate absorption of aumolertinib or osimertinib.

- **Note:** At the discretion of the Investigator, selected participants with a PEG tube may be eligible for this study. For any such participant, the PEG must allow for the safe and adequate administration of tablets (ie, without crushing or otherwise damaging them).

2. Has evidence, and/or a past medical history, of interstitial lung disease; drug-induced interstitial lung disease; radiation pneumonitis that required steroid treatment; or clinically active interstitial lung disease.

3. Has evidence of any active bacterial infection, fungal infection, or viral infection (including SARS-CoV-2, as detailed below) which would preclude safe enrollment, as assessed by the treating Investigator.
    - **Note:** There are no protocol-specified testing requirements for SARS-CoV-2 in this study. SARS-CoV-2 requirements are instead determined by institutional standards (and local/country regulations, as applicable) and Investigator judgment.
        - At Investigator discretion, any participant who tests positive and/or is symptomatic for SARS-CoV-2 during Screening may either be excluded from the study or delay enrollment until active infection has been excluded per institutional standards.
        - During the study, any SARS-CoV-2 testing is to be performed as clinically indicated for the individual participant. The Investigator must document the results of all tests performed. Any confirmed infection is to be recorded as an AE or, in the event that clinical manifestation warrants such, recorded and handled as an SAE as detailed in Section 10.2.4.
4. Has, or shows evidence of, any other active infection; significant medical illness; serious underlying medical condition; abnormal laboratory finding; or psychiatric illness/social situation that might, in the Investigator's judgment, prevent the participant from receiving study treatment or being followed in this study, or which otherwise renders the participant inappropriate for the study, as judged by the Investigator.
5. Hypersensitivity or allergy to aumolertinib or osimertinib or their excipients.

Prior/Concomitant Therapy

6. Has received prior systemic treatment for metastatic NSCLC.
    - **Notes:**
        - Prior chemotherapy is permitted, provided that it was used for treatment of locoregional NSCLC as a component of curative intent therapy **and** administration was completed more than 6 months prior to Screening.
        - Participants with a history of radiotherapy may be eligible (with a required washout period of ≥ 2 weeks before Screening, as detailed in Inclusion Criterion #9 above); however:
            - Concurrent radiotherapy is **not** permitted.
        - Prior EGFR-TKI therapy is **not** permitted.
7. **For participants in the aumolertinib monotherapy and aumolertinib with chemotherapy arms:** Use of any prohibited concomitant medications, as outlined in Section 6.7 and Section 10.5; this includes use of any strong CYP3A4 inhibitors/inducers within approximately 14 days (or 5 half-lives) before Day 1 and use of any grapefruit or grapefruit-containing products within 72 hours before Day 1 through the participant's final study visit.

- **Note for participants in the osimertinib monotherapy and aumolertinib with chemotherapy arms:** Guidance concerning prohibited concomitant medications is to be followed per the current prescribing information for osimertinib, pemetrexed, cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, or gemcitabine, as applicable; institutional standard of care; and (as applicable) local regulations.

Diagnostic Assessments

8. Is a candidate for curative intent therapy for the NSCLC diagnosis.
9. Tumor has mixed small-cell and non-small cell pathology.
10. Has a history of prolonged QT syndrome or Torsades de Pointes.
11. Meets any of the following cardiac criteria:
    - Has any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, including evidence of QT prolongation.
    - Has any factor, including any current medication(s), known to increase the risk of QTc prolongation or the risk of arrhythmic events.
      - **Note:** Bundle branch block (BBB) is a correction factor for QTc prolongation. Thus, QTc is corrected based on the institutional criteria in the presence of BBB.

5.3. Lifestyle Considerations

To reduce the probability or severity of skin reactions, protection from sunlight is recommended from the start of treatment with aumolertinib until 3 to 4 weeks after discontinuation of aumolertinib treatment.

5.3.1. Meals and Dietary Restrictions

Consumption of grapefruit or grapefruit-containing products is prohibited from 72 hours before Day 1 through the participant's final study visit.

5.3.2. Activity

Participants are to abstain from strenuous exercise for 4 hours before each blood collection performed for the study clinical laboratory tests.

5.4. Screen Failures

A screen failure occurs when a participant who consents to enroll in the clinical study is not subsequently randomized. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants in order to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information for this study will include informed consent date, demography, screen failure details, eligibility criteria, and any SAE(s).

Individuals who do not meet the criteria for participation in this study within 28 days (screen failures) are not enrolled. Previously screened participants may undergo one (1) additional re-screening for screen failure purposes and to confirm eligibility for study participation. The Investigator should confirm any such re-screening with the Sponsor.

Any re-screened participants should be assigned a different participant number.

- **Note:** The Investigator may recommend that prospective study participants for whom EGFR mutation testing is not covered or reimbursed by standard of care undergo such testing for confirmatory purposes pre-screening (refer to Appendix 9 [Section 10.9]).
  - Any such individual will be required to sign the separate Pre-Screening Informed Consent Form to allow this testing.
  - After signing the form, the participant will proceed to full screening if the test results confirm that a required EGFR mutation is present and the participant agrees to join the study by signing the main study Informed Consent Form.
  - Without a confirmed EGFR mutation, prospective participants will **not** be eligible to participate in the study and will **not** be considered screen failures.

5.4.1. Screening and Enrollment Log and Participant Identification Numbers

Each participant's enrollment in the study will be recorded in the screening and enrollment log.

Upon provision of signed informed consent, each participant will receive a unique participant identification number. This number is assigned by the IRT system. Participant numbers will not be re-used for different participants.

6. STUDY INTERVENTIONS AND CONCOMITANT THERAPY

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

6.1. Study Interventions Administered

Aumolertinib (as two 55-mg tablets) is to be administered once daily, and may be administered with or without food. (Of note, glucose is to be obtained in the fasted state for the Screening serum chemistry lab collection [refer to the applicable SoA in Section 1.3], but non-fasted at all other time points.) Each participant should be given instructions to maintain approximately the same daily time of aumolertinib administration to ensure a similar interval between doses.

Osimertinib (as single 80-mg tablet) is to be administered once daily in accordance with the current osimertinib prescribing information and institutional standard of care.

Administration of the other study interventions is to occur in accordance with the current prescribing information for pemetrexed, cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, or gemcitabine, as applicable, and with institutional standard of care.

Table 4: Study Treatment Arms

Arm Title:	**Aumolertinib monotherapy arm**	**Aumolertinib with chemotherapy (combination) arm**, consisting of either: ***For adenocarcinoma:*** aumolertinib + either cisplatin **or** carboplatin, along with pemetrexed **OR** ***For squamous cell carcinoma:*** aumolertinib + either cisplatin or carboplatin, along with one of the following: paclitaxel, albumin-bound paclitaxel, or gemcitabine[a]	**Osimertinib monotherapy arm**
Arm Type:	Investigational	Investigational	Active comparator
Arm Description:	Not applicable	Participants randomized to receive aumolertinib with chemotherapy will receive up to 4 cycles of a platinum-based doublet along with once-daily aumolertinib administered at 110 mg. Thereafter, at the Investigator's discretion, participants may go on to receive maintenance pemetrexed along with once-daily aumolertinib,[b]	Not applicable
Associated Intervention Label:	Two 55-mg tablets taken orally, QD	Two 55-mg tablets taken orally, QD	Single 80-mg tablet taken orally, QD

[a] Paclitaxel is to be given over 4 to 6 (fixed) cycles of treatment; this is the only study chemotherapy drug that may be administered for up to 6 cycles. Carboplatin/carboplatin-containing chemotherapy is to be given over 4 fixed cycles (q3wk × 4 cycles).

[b] If the Investigator considers it to be of continued clinical benefit for the individual participant, pemetrexed will be given as maintenance therapy for the remainder of the participant's time on study treatment—provided the participant does not meet any of the study treatment discontinuation and/or overall study discontinuation criteria.

q3wk = once every 3 weeks; QD = once daily.

6.2. Preparation, Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions will be provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Type of Study	Measures
Open-label, using permuted block central randomization via IVRS/IWRS	This is an open-label study; however, the specific intervention to be taken by a participant will be assigned using an IVRS/IWRS and integrated into the EDC on the proper case report form. The site will contact the IVRS/IWRS prior to the start of study intervention administration for each participant. Potential bias will be reduced by permuted block randomization. Site is not a stratification factor for this study.

EDC = electronic data capture; IVRS = interactive voice response system; IWRS = interactive Web response system.

6.4. Study Intervention Compliance

When participants are dosed at the study site, they will receive study intervention directly from the Investigator or designee under medical supervision. The date and time of each dose of study intervention administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. For orally administered study intervention, study site staff will examine each participant's mouth to ensure that the study intervention was ingested.

When participants orally self-administer study intervention(s) at home, compliance with the study intervention will be assessed at each visit. Compliance with orally administered study intervention will be assessed by counting returned tablets during the site visits and documented in the source documents and relevant form. Any deviation(s) from the prescribed dosage regimen should be recorded.

The Investigator should consult with the Sponsor regarding any suspected treatment compliance issues in the study.

A record of the quantity of all study interventions dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded.

6.5. Dose Modification

Any toxicity observed with aumolertinib could be managed by dose reductions of that study intervention, as specified in Table 5. If the aumolertinib dose has been reduced to the minimum, but the participant is still unable to tolerate the drug, termination of treatment is recommended.

Dose reduction of any of the other study interventions is to be performed in accordance with the current local label for osimertinib, pemetrexed, cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, or gemcitabine, as applicable, and with institutional standard of care.

For participants in the aumolertinib with chemotherapy arm who have any of the component agents held or discontinued due to safety/toxicity concerns, treatment with the other agent(s)—whether aumolertinib or chemotherapy—may be continued at the discretion of the Investigator. Participants who have one chemotherapy agent discontinued may continue on the other agent, as well as aumolertinib, per Investigator discretion.

Table 5: Specifications for Aumolertinib Dose Reduction

	Initial Treatment	First Dose Reduction Treatment
Dose:	110 mg/day aumolertinib	55 mg/day aumolertinib
Drug:	Aumolertinib active, 55 mg, 2 tablets	Aumolertinib active, 55 mg, 1 tablet
Frequency, Method of Administration:	QD, PO	QD, PO

PO = orally; QD = once daily.

6.5.1. General Principles of Aumolertinib Dose Adjustment Related to Selected AEs

Refer to Section 2.3.1 and to the current aumolertinib IB for information regarding risks that may be associated with aumolertinib.

If a participant experiences a) an AE that is, as judged by the Investigator, NCI CTCAE Grade 3 or higher in severity; **and/or** b) an AE of any grade that is considered unacceptable by the Investigator—and the Investigator assesses the event(s) as treatment-related—dosing will be withheld and supportive care will be given in accordance with local practice/guidelines, as needed.

- **Note:** "Treatment-related" here can be explained as definitely related, probably related, or possibly related to study treatment per Investigator assessment, but excluding unlikely related and not related.

Aumolertinib dose adjustment guidelines are specified in Table 6. These guidelines apply to participants in the aumolertinib monotherapy arm and the aumolertinib with chemotherapy arm.

Table 6: Dose Adjustment Principles of Aumolertinib Tablets when Selected AEs Considered Treatment-related by the Investigator Occur

Type	AEs Considered Related to Study Treatment with Aumolertinib	Dose Adjustment[a]
All	Any treatment-related AE of ≥ Grade 3 severity not addressed elsewhere in this table	**Unless otherwise instructed within this table:** Hold study treatment for up to 3 weeks; • If the AE improves to ≤ Grade 2, resume treatment. – Resume treatment at 110 mg for the first occurrence. – Resume treatment at 55 mg for the second occurrence. • If the AE has not improved to ≤ Grade 2 after 3 weeks, permanently discontinue aumolertinib.
Heart	At least 2 independent ECG examinations have found that the QTc interval is greater than 500 ms.	Hold study treatment for up to 3 weeks; • If the baseline[b] value is > 470 ms, and the QTc interval is improved to baseline within 3 weeks, resume treatment at 55 mg. • If the baseline value is ≤ 470 ms, and the QTc interval is improved to ≤ 470 ms within 3 weeks: – Resume treatment at 110 mg for the first occurrence. – Resume treatment at 55 mg for the second occurrence. If the QTc interval remains > 500 ms after study treatment has been held for 3 weeks, permanently discontinue aumolertinib.
	QTc prolongation combined with any of the following: • Torsades de Pointes • polymorphic ventricular tachycardia • signs or symptoms of serious arrhythmia	Permanently discontinue aumolertinib.
	Absolute decrease from baseline in asymptomatic LVEF > 10% and associated absolute value < 50%	Hold study treatment for up to 3 weeks; If improved to baseline LVEF within 3 weeks: • Resume treatment at 110 mg for the first occurrence. • Resume treatment at 55 mg for the second occurrence.
	Symptomatic congestive heart failure	Permanently discontinue aumolertinib.

Type	AEs Considered Related to Study Treatment with Aumolertinib	Dose Adjustment[a]
Liver dysfunction	Abnormal liver function as described in Section 10.4	Hold study treatment for up to 3 weeks; If ALT and/or AST improve(s) to ≤ Grade 1 and TBIL improves to ≤ Grade 1 within 3 weeks: • Resume treatment at 110 mg for the first occurrence. • Resume treatment at 55 mg for the second occurrence. Permanently discontinue aumolertinib if: • ALT and/or AST > 8 × ULN any one time; **or** • ALT and/or AST > 5 × ULN for more than 2 weeks; **or** • ALT and/or AST > 3 × ULN and TBIL > 2 × ULN.
Cornea	Corneal ulcer	Permanently discontinue aumolertinib.
Permanent discontinuation of aumolertinib should be considered if, at any time, the participant is unable to tolerate 55 mg (≥ Grade 3 adverse reactions).		

Note: All grades described in this table refer to severity grading using NCI CTCAE version 5.0.
[a] The recommendations herein are general guidance principles. The final course of action can be modified by the Investigator in concert with the Medical Monitor.
[b] The Screening QTc interval in this study is considered the baseline QTc interval.
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QTc = corrected QT interval; TBIL = total bilirubin; ULN = upper limit of normal.

6.5.2. Dose Adjustments to Osimertinib or Chemotherapy Regimens

The doses of osimertinib and the protocol-permitted chemotherapy regimens in this study are permitted to be adjusted in response to AEs considered treatment-related by the Investigator.

Any such dose adjustments are to be performed in accordance with the current local label for osimertinib, pemetrexed, cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, or gemcitabine (as applicable), and with institutional standard of care.

If an AE is considered by the Investigator to be related to treatment with only one study intervention, dose adjustment only applies to that study intervention.

As noted previously, participants in the aumolertinib with chemotherapy arm who have had any of the component agents held or discontinued due to safety/toxicity concerns may continue on the other agents (aumolertinib or chemotherapy) at the discretion of the Investigator. Participants who have one chemotherapy agent discontinued may continue on the other agent, as well as aumolertinib, per Investigator discretion, and no delay in aumolertinib dosing is necessitated by a delay in chemotherapy drug dosing.

The Investigator should reach a consensus with the Medical Monitor on the appropriate next steps for any participant who undergoes an osimertinib or chemotherapy dose adjustment.

The time window of each dose of chemotherapy is calculated from the date of the last dose. Before each chemotherapy cycle of a protocol-permitted chemotherapy regimen, the treating Investigator should follow institutional guidelines and best clinical practice in interpreting the required laboratory data, and then deciding on the dosing and timing of chemotherapy administration.

For some participants, the Investigator may decide, due to benefit/risk considerations, to administer chemotherapy after a delay of more than 1 week. Whenever possible, the Investigator should review the applicable circumstances with the Medical Monitor before administering chemotherapy to such participants.

If the above criteria for starting chemotherapy are not met, or if the delay in chemotherapy administration exceeds 21 days, the Investigator should reach a consensus with the Medical Monitor on the appropriate next steps for the individual participant.

Overlapping Toxicities of Aumolertinib and Chemotherapy

Concomitant administration of aumolertinib with potent inhibitors of CYP3A4 enzymes may increase blood CPK, as discussed in the current aumolertinib IB and in the Hansoh package insert for aumolertinib mesylate tablets. This potential toxicity has been addressed in the EQ143-301 (TREBLE) study by the exclusion criteria (Section 5.2) which prohibit the participation of individuals who have used strong CYP3A4 inhibitors within approximately 14 days before Day 1 of the trial.

Potential risks of aumolertinib that overlap with the known risks of chemotherapy in this study include gastrointestinal toxicity (including diarrhea, nausea, and vomiting); skin disorders (such as rash); respiratory disorders (such as interstitial lung disease); myelosuppression; ocular disorders; and hepatic disorders. Refer to the current aumolertinib IB for all available safety data.

In the case of overlapping toxicity, the Investigator should use clinical judgment when attributing a toxicity to one or more of the study interventions and consider following the more conservative approach.

6.5.2.1. Recommendations for Discontinuing Osimertinib or Chemotherapy

Some participants in this study may require discontinuation of osimertinib or a protocol-permitted chemotherapy regimen (eg, for toxicities considered treatment-related by the Investigator). Any such discontinuation is to be performed in accordance with the current prescribing information for osimertinib, pemetrexed, cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, or gemcitabine (as applicable), and with institutional standard of care.

The Investigator should reach a consensus with the Medical Monitor on the appropriate next steps for any participant who discontinues osimertinib or a protocol-permitted chemotherapy regimen.

6.6. Treatment of Overdose

In the context of a clinical study, an overdose is any dose which exceeds the daily dose that is defined in the clinical study protocol. Thus, for this study, any dose of aumolertinib greater than 110 mg within a 24-hour time period will be considered an overdose. Symptoms of aumolertinib overdose are not established, and there is no specific treatment for such an overdose.

Overdoses of any of the other study interventions should be determined by the current prescribing information for osimertinib, pemetrexed, cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, or gemcitabine (as applicable), and by institutional standard of care.

In the event of any overdose of any study intervention in this trial, the Investigator should take the following steps:

- Contact the Medical Monitor immediately (within no more than 24 hours of awareness). The designated Sponsor representative will work with the Investigator to ensure that all relevant information is provided to the Sponsor or designee.
- Document the quantity of the excess dose, as well as the duration of the overdose.
- Withhold the study intervention and closely monitor the participant for any AEs/SAEs and/or laboratory abnormalities.
  - **Note:** For overdoses associated with an AE/SAE, the standard reporting timelines apply as detailed in Section 10.2.
- Obtain a plasma sample for PK analysis as soon as possible.
- Follow general supportive measures and treat symptomatically.

Overdoses of any study intervention other than aumolertinib should be treated in accordance with the current prescribing information for osimertinib, pemetrexed, cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, or gemcitabine, as applicable, and with institutional standard of care.

6.7. Prior and Concomitant Therapy/Procedures

The Investigator or qualified designee will review participants' prior medication use, including prescription medications and over-the-counter preparations, and record prior medications taken by the participant within 28 days prior to the first day of Screening.

Concomitant therapy is defined as any medication (other than study intervention) that was used at least once after the administration of study intervention.

- If a clear determination cannot be made (partial medication end dates), the medication will be classified as concomitant.
- Any vaccine administration that occurs during the study will recorded as a concomitant medication.

- Any SARS-CoV-2 testing during the study will be performed if clinically indicated per the Investigator, in accordance with institutional standards (and, if applicable, local/country regulations), and will be recorded as a laboratory procedure as detailed in the applicable SoA (Section 1.3). Any positive result is to be recorded and handled as an AE (or, if clinical manifestation warrants such, as an SAE) in accordance with Section 10.2.
- Any treatment known to prolong the QTc interval will not be allowed.
- Participants must refrain from using any prohibited concomitant medications, as outlined in Section 10.5.
- If a clear determination cannot be made (partial medication end dates), the medication will be classified as concomitant.
- The Investigator or qualified designee will record any medication(s) taken by the participant, and any procedure(s) performed (as applicable), during the participant's time on study through the last study visit. Documentation will include information regarding start and stop dates, dose(s), and reasons for the medication use.
- All participants must adhere to the following washout period requirements for protocol-permitted prior anticancer therapies (refer to Section 5.1 and Section 5.2):
  - Major surgery: 4 weeks before Screening
  - Chemotherapy: 6 months before Screening
  - All other permitted therapies, including permitted radiotherapy (refer to Exclusion Criterion #6 in Section 5.2): 2 weeks before Screening

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION FROM STUDY TREATMENT AND FROM THE OVERALL STUDY

Discontinuation of specific study sites is handled as part of the appendix on governance (refer to Section 10.1.9.3).

Refer to Section 7.4 for criteria that may potentially result in the Sponsor reviewing the evaluable data and considering whether study stoppage (permanent discontinuation) may be appropriate.

7.1. Permanent Discontinuation of a Participant from Study Treatment

It may be necessary for a participant to permanently discontinue from study treatment (all 3 arms). Should such permanent discontinuation of study treatment occur, the participant will remain in the study for safety and survival follow-up, provided that overall consent has not been withdrawn. Refer to the applicable SoA (Section 1.3) for data to be collected at the time of the participant's discontinuation from study treatment and during subsequent follow-up.

A participant's study treatment will be permanently discontinued if any of the following occurs during the study:

- The participant experiences disease progression as assessed by the Principal Investigator or sub-Investigator and agreed to by the Sponsor Medical Monitor following consultation, **except** in the following scenario:
  - If it is the medical opinion of the Investigator that continuation of assigned study treatment would provide clinical benefit to a participant whose disease progression is confirmed, that participant may continue therapy upon discussion with the Sponsor, provided that **both** of the following criteria are met. Any such participant will also be required to sign a separate ICF:
    - No decline in ECOG PS attributable to underlying disease.
    - Absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression).
  - For all participants, all tumor imaging assessments—including brain imaging assessments, if applicable—are to continue at the scheduled interval of every 6 weeks (± 3 days) for the first 3 post-baseline assessments (with "baseline" defined as the participant's most recent scan performed prior to the first dose of any study intervention and within 28 days before Day 1 of Cycle 1), then every 12 weeks (refer to the applicable SoA [Section 1.3]), regardless of any treatment delays.
- The participant suffers an AE which, in the judgment of the Investigator, Sponsor, or Medical Monitor, presents an unacceptable risk to the participant.
- General or specific changes in the participant's condition (eg, a significant intercurrent illness or complication) which, in the judgment of the Investigator, renders further administration of study intervention unacceptable for the participant.

- The participant has either of the following:
  - Liver toxicity, as noted in Section 7.1.1 and defined in Section 10.4; **or**
  - Appearance of a corneal ulcer.
- Occurrence of pregnancy in a female study participant or female partner of a male study participant (as applicable).
- Significant noncompliance of the participant with protocol requirements.
- The Sponsor, or legal representative of the Sponsor, requests the participant to withdraw.
- The participant is lost to follow-up (must have at least 3 documented attempts to contact the participant; refer to Section 7.3).
- The participant exhibits any evidence of drug abuse in the opinion of the Investigator.
- Permanent study treatment discontinuation is judged by the Investigator to be in the best interest of the participant.
- The participant withdraws consent for the study.
- The Sponsor makes the decision to terminate the site or study.

In the event of a participant discontinuing from study treatment without withdrawing overall consent, that participant should be strongly encouraged to complete all protocol-scheduled assessments—including safety and survival follow-up—as detailed in the applicable SoA (Section 1.3).

Whenever possible, any participant who discontinues from study treatment for a reason other than progression of disease should have a CT scan of the chest and abdomen/pelvis with contrast (or a PET/CT scan, if that is the imaging modality used for the individual participant per Investigator discretion) performed, provided that they have not undergone a scan within the prior 4 weeks.

The Investigator will document the reason for each participant's discontinuation from study treatment on the applicable eCRF page.

When a participant's study treatment discontinuation is due to either an SAE or a Grade 3 or 4 toxicity (regardless of seriousness) that is considered treatment-related by the Investigator, the Investigator should follow the event until resolution, stabilization, or it is deemed that further recovery is unlikely. Data on all such events should be collected in the AE section of the eCRF.

In the event that a participant discontinues from study treatment due to an AE (or SAE, as applicable), the Investigator should notify the Medical Monitor or Pharmacovigilance representative by email within 24 hours of treatment discontinuation. All SAEs in the study are to be recorded and handled as detailed in Section 10.2.4.

In the event of a pregnancy (of a female study participant or female partner of a male study participant) during the study, the Investigator is to record pregnancy information on the Pregnancy Reporting and Outcome Form and submit the completed form to the Sponsor within 24 hours as detailed in Section 8.4.5.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study treatment in response to abnormal liver test results is required by the Investigator a) when a participant meets one of the conditions outlined in Section 10.4, **or** b) in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, if the Investigator believes that this is in the best interest of the participant.

7.1.2. Cardiac Stopping Criteria

If a clinically significant cardiac finding is identified after study enrollment—eg, any Grade 4 cardiac AE or any Grade 3 QTc prolongation event that is not resolved within 3 weeks (refer to Table 6)—the Investigator or qualified designee will determine if the participant can continue on study treatment or must be permanently discontinued from treatment.

The review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE per Section 10.2.3.

7.1.3. Temporary Discontinuation of a Participant from Study Treatment

A participant may temporarily discontinue from study treatment with any study intervention for a duration of up to 3 weeks, for any reason. However, any such temporary discontinuation must be reported to the Medical Monitor, and the participant's study assessments must continue as specified in the applicable SoA (Section 1.3).

If treatment with any study intervention is temporarily discontinued for any participant, it may be re-started within the aforementioned 3-week period at the discretion of the Investigator with notice to the Medical Monitor.

Beyond a duration of 3 weeks, the participant **may not** re-start study treatment and will be permanently removed from the study.

7.1.4. Re-challenge Therapy

Re-challenge (re-introduction) may be initiated with any study intervention in participants whose temporary discontinuation of study treatment has occurred within ≤ 3 weeks—provided that, in the opinion of the Investigator, the benefits of continuing the participant's study treatment outweigh the risks.

If treatment with any study intervention has been discontinued due to toxicity, the Investigator must confirm the toxicity is resolving (to at least ≤ Grade 2 severity) before attempting re-challenge.

If treatment with any study intervention has been discontinued for any other reason, that reason must be provided to the Medical Monitor.

7.2. Permanent Discontinuation/Withdrawal of a Participant from the Study

Participants may permanently discontinue/withdraw from the study at any time at their own request or may be permanently discontinued/withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. Any such participant will be permanently discontinued from study treatment **and** from the overall study at that time.

If a participant withdraws consent for disclosure of their future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent, subject to any limitations under applicable data privacy and data protection laws.

If a participant permanently discontinues/withdraws from the study, they may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Refer to the applicable SoA (Section 1.3) for details of the data to be collected at the time of study discontinuation.

7.2.1. Criteria for Permanent Participant Discontinuation/Withdrawal from the Study

All participants should be encouraged to complete all study evaluations. However, participants may withdraw overall consent for participation in this study at any time without penalty or loss of benefits to which they are otherwise entitled.

Every reasonable effort should be made to determine the reason a participant withdraws study consent, and this information should be recorded on the appropriate page(s) of the eCRF.

Where participants discontinue study treatment prematurely without withdrawing overall consent, reasonable efforts should be made to perform all protocol-specified assessments in order to avoid losing outcome data that is necessary for the evaluation of safety.

Participants may withdraw from the study at their own discretion (or be withdrawn at the discretion of the Investigator) for any reason, at any time.

The reasons participants may be withdrawn from the study may include, but are not limited to, the following:

- Occurrence of an AE that in the opinion of the Investigator, warrants the participant's permanent withdrawal from the study.
  - In the event of permanent withdrawal due to the occurrence of a nonserious AE, the study site should notify the Sponsor or Sponsor's representative as soon as possible.
  - In the event of permanent withdrawal due to the occurrence of an SAE, the Medical Monitor or representative must be notified within 24 hours as specified in Section 10.2.4.
- Significant noncompliance, defined as refusal or inability to adhere to the prescribed dosing and follow-up regimen.
- Request of the participant, Investigator, or study Sponsor.
- Participant withdraws informed consent.
- Participant is lost to follow-up (must have at least 2 documented attempts to contact the participant; refer to Section 7.3).
- Death.

All data and laboratory samples collected prior to the date on which the participant's consent is withdrawn will remain in the clinical database and at the laboratory vendor.

7.3. Lost to Follow-up

Participants will be considered lost to follow-up if they repeatedly fail to return for scheduled study visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible (and within the visit window, where one is defined in the applicable SoA [Section 1.3]); counsel the participant on the importance of maintaining the assigned visit schedule; **and** ascertain whether the participant wishes to, and/or should, continue in the study.
- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant—where possible, 2 telephone calls and, if necessary, a certified letter to the participant's last known mailing address, or local equivalent methods—and to regain any remaining study intervention from the participant. The Investigator should be making every effort to collect any unused medication, and these contact attempts should be documented in the participant's medical record.
- Should the participant, and/or caregiver authorized to serve as a contact for the participant (as applicable), continue to be unreachable, that participant will be considered to have withdrawn from the study.
- For all participants enrolled in the study, site personnel or an independent third party will attempt to collect the vital status of the participant within legal and ethical boundaries. Public sources may be searched for vital status information. If a participant's vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

A participant will be considered lost to follow-up after 3 months of documented unsuccessful contact attempts.

7.4. Criteria for Potential Stoppage (Permanent Discontinuation) of the Study

The Sponsor will review the evaluable data—including any emerging safety signals attributed to the study drug—and will consider whether the permanent stoppage (discontinuation) of the study may potentially be appropriate.

As noted in Section 4.4, stoppage (permanent discontinuation) of the study may also occur in any of the following circumstances:

- Overall, country-/region-specific, or site-specific stoppage by the Sponsor at any time, for any reason
- Stoppage in a specific country or region by the relevant Health Authority

- Stoppage at a specific site by the relevant IRB/IEC or by the Principal Investigator (refer to the relevant portion of the appendix on governance [Section 10.1.9.3])

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their associated timing are summarized in the SoAs for each treatment arm (Section 1.3).

Protocol waivers or exemptions are not permitted.

Additional Information

- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine the appropriate course of action for the individual participant.
- Adherence to the study design requirements, including those specified in the SoAs (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the individual participant's routine clinical management (eg, blood count) and obtained before the provision of signed informed consent may be utilized for screening or baseline purposes, provided that the procedures met the protocol-specified criteria and were performed within the timeframe defined in the applicable SoA (Section 1.3).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra (ie, repeat or unscheduled) assessments that may be required, is not expected to exceed 300 mL. Refer to Section 8.7 for details.

Medical History

For all participants, a medical history will be obtained by the Investigator or qualified designee. The medical history will collect all medical and surgical conditions which the Investigator considers to be clinically significant and relevant for the individual participant.

Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

Calibration of Equipment

The Investigator (or qualified designee) is responsible for ensuring that any device or instrument used for a clinical evaluation/test during the study that provides information about eligibility criteria, and/or safety or efficacy parameters, is suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Equipment calibration documentation is to be retained at the study site and available for inspection.

8.1. Efficacy Assessments

Planned time points for all study efficacy assessments are presented (by treatment arm) in the SoAs (Section 1.3).

8.1.1. Antitumor Activity Assessments

RECIST v1.1 guidelines (Eisenhauer 2009) will be used for all tumor assessments in the study, as detailed in Section 10.6.

In addition, assessments of brain metastases will follow RANO criteria as detailed in Section 10.7.

8.1.2. Tumor Imaging Assessments

8.1.2.1. Computed Tomography Scans of the Chest and Abdomen/Pelvis with Contrast

CT scan of the chest and abdomen/pelvis (covering the liver and adrenal glands) with contrast is the preferred imaging modality for the study. (PET/CT may be used for an individual participant at Investigator discretion; refer to Section 8.1.2.2.)

Scans should be contiguous throughout the anatomic region of interest.

The most critical CT image acquisition parameters for optimal tumor evaluation using RECIST v1.1 (refer to Section 10.6) are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

8.1.2.2. Positron Emission Tomography/Computed Tomography Scans

As noted above in Section 8.1.2.1, CT with contrast is the preferred imaging modality for use in the study; however, PET/CT may instead be used for an individual participant at the discretion of the Investigator. **The same imaging modality (CT with contrast or PET/CT) should be used across all tumor assessment scan collections for the individual participant.**

Bone lesions that are identified on any PET/CT scan performed at baseline and are confirmed by CT or X-ray should be recorded as nontarget lesions and followed by the same method as per the baseline assessment.

PET/CT scans may be used as a method of assessment to identify the presence of new bone lesions during follow-up.

New lesions will be recorded where a positive hot spot that was not present on the baseline scan assessment is identified on a PET/CT scan performed at any time during the study. The Investigator should consider the positive hot spot to be a significant new site of malignant diseases and to represent true disease progression in order to record the new lesion.

Confirmation by CT and X-ray is recommended where PET/CT scan findings are equivocal.

8.1.2.3. Anatomic Coverage

Optimal anatomic coverage for most solid tumors is the chest, abdomen, and pelvis.

Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual participants.

Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up time points. This will enable better consistency of not only tumor measurements, but also identification of new disease.

8.1.2.4. IV Contrast Administration

Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdominal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given participant. It is very important that the same technique be used at baseline and on follow-up examinations.

For participants who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) should be performed should also be based on the tumor type and anatomic location of the disease and should be optimized to allow for comparison to prior studies, if possible.

Each case should be discussed with the radiologist to determine if substitution of the other approaches is possible and, if not, the participant should be considered not evaluable from that point forward.

Care must be taken in the measurement of target lesions on a different modality and the interpretation of nontarget disease or new lesions because the same lesion may appear to have a different size using a new modality. Oral contrast is recommended to help visualize and differentiate structures in the abdomen.

If iodinated contrast is medically contraindicated at baseline or at any time during the study, the recommended approach is chest CT without contrast and PET/CT of the abdomen and pelvis.

If PET/CT is not available, CT without IV contrast is the choice for one of the chest, abdomen, and pelvis collections.

For assessment of brain lesions, MRI is the preferred method; CT may be used if MRI is medically contraindicated. Refer to Section 8.1.2.7 for details.

8.1.2.5. Slice Thickness and Reconstruction Interval

It is recommended that CT scans be performed at 5-mm contiguous slice thickness or less; this guideline presumes a minimum 5-mm thickness in recommendations for measurable lesion definition. Occasionally, institutions may perform medically acceptable scans at slice thicknesses greater than 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

All CT window settings should be included, particularly in the thorax, where the lung and soft-tissue windows should be considered.

The target lesions are measured by use of the same window settings for repeated examinations throughout the study.

All images from each examination should be included and not "selected" images of the apparent lesion.

8.1.2.6. Sites and Schedule of Tumor Assessments

If a participant is found to have brain lesions, or metastatic lesions in other sites, on baseline imaging, tumor assessments must be performed on the corresponding site(s) during each subsequent follow-up.

All tumor assessments are to be performed per RECIST v1.1 (refer to Section 10.6). Additionally, all brain metastases are to be assessed per RANO criteria (refer to Section 10.7).

For participant and Investigator/site convenience in this study, tumor assessments are scheduled to occur in parallel every 6 weeks ± 3 days for the first 3 post-baseline assessments (with "baseline" defined as the participant's most recent scan performed prior to the first dose of any study intervention and within 28 days before Day 1 of Cycle 1), and then every 12 weeks thereafter. Scans will be reviewed centrally.

Sites with no metastasis at baseline (for example, no brain or bone metastases) need not be evaluated during subsequent follow-ups, per Investigator discretion.

Additional imaging examinations are to be performed at Investigator discretion, as clinically indicated (i.e, based on individual participant signs and/or symptoms).

Whenever possible, any participant who discontinues from study treatment for a reason other than disease progression should have a CT with contrast (or PET/CT, if that has been the participant's imaging modality throughout the study per Investigator discretion) performed if they have not undergone a scan within the prior 4 weeks.

Note that all tumor imaging assessments are to be performed at the scheduled interval of every 6 weeks (± 3 days) for the first 3 post-baseline assessments and then every 12 weeks, regardless of whether the participant's treatment cycle is delayed.

8.1.2.7. Brain Imaging

Brain imaging is to be performed as indicated in the applicable SoA (Section 1.3). As with all other tumor imaging assessments in the study, brain imaging assessments are to be performed at the scheduled interval regardless of any treatment delays.

CT and MRI are generally considered to be the best currently available and reproducible methods to measure target lesions selected for response assessment, and to assess nontarget lesions and identify new lesions.

For assessment of brain lesions, MRI is the preferred method; CT scans may be used if MRI is medically contraindicated.

As noted in the applicable SoA (Section 1.3), baseline brain imaging must be performed within 28 days before the start of study treatment. Ideally, these scans should be performed as close in time as possible to the start of study treatment. Additional imaging examinations can be performed based on individual participant signs and/or symptoms.

8.1.3. ECOG Performance Status

The assessment of ECOG PS will be performed following the grading described in Table 7.

Table 7: Eastern Cooperative Oncology Group Performance Status

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

ECOG = Eastern Cooperative Oncology Group; PS = performance status.
Source: Oken 1982

8.1.4. Post-treatment Circulating Tumor DNA Clearance

Post-baseline ctDNA will be assessed via validated assay, using blood samples of approximately 20 mL each. These samples will be collected as per the applicable SoA (Section 1.3), including at the time of disease progression (as applicable). ctDNA samples will then be sent to the central laboratory for processing.

8.1.5. Companion Diagnostic Testing

Confirmed presence of a required EGFR mutation is a requirement for all participants in the EQ143-301 (TREBLE) study. For screening and enrollment purposes, results of a clinically validated assay—using a licensed laboratory/laboratory with applicable local accreditation—will be acceptable to confirm the presence of such a mutation in the blood or tissue. If available, existing EGFR mutation test results may be used to confirm participant eligibility, provided that they were obtained within ≤ 3 months prior to study entry.

- If recommended by the Investigator, prospective study participants for whom EGFR mutation testing is not covered or reimbursed by standard of care may undergo confirmatory testing pre-screening.
  - Any such prospective participant will be required to sign a separate Pre-Screening ICF, as detailed in Appendix 9 (Section 10.9). This ICF will allow blood or tissue sample collection to be performed for local EGFR mutation testing prior to the 28-day study Screening window.

All participants in the study will also have a blood sample for central retrospective testing collected predose on Day 1 of treatment Cycle 1.

If archival tumor tissue (FFPE or unstained slides) is available (regardless of when it was obtained), and the participant agrees to provide this tissue by completing the applicable section of the main study ICF, it will also be collected during Screening; however, this is not mandatory.

8.2. Safety Monitoring

Phase 1 and 2 clinical studies have shown that aumolertinib monotherapy is well tolerated at an oral dose of 110 mg daily, with no unexpected toxicity events. In addition, a Phase 3 randomized, controlled, open-label, multicenter study is currently ongoing to compare the efficacy and safety of aumolertinib monotherapy versus aumolertinib in combination with platinum-containing doublet chemotherapy; no unexpected safety findings have been reported.

Safety monitoring in the EQ143-301 (TREBLE) study will be conducted from the time participant signed informed consent is provided through the time points indicated in the applicable SoA (Section 1.3). Routine safety evaluations will include monitoring of AEs/SAEs, vital sign measurements, physical examinations, 12-lead ECGs, and clinical laboratory assessments (including hematology, serum chemistry, urinalysis, and coagulation, which are to be collected by local laboratory as detailed in Section 8.3.4).

Additional safety evaluations will be performed at the discretion of the Investigator with the oversight of the Medical Monitor.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the applicable SoA (Section 1.3).

The toxicity of all study interventions will be assessed by the Investigator per NCI CTCAE version 5.0.

8.3.1. Physical Examinations

8.3.1.1. Full and Symptom-directed Physical Exams

Full physical examination evaluations at Screening should include general appearance; skin; neck; eyes; ears; nose; throat; lungs; heart; abdomen; back; lymph nodes; extremities; and neurological examinations. Subsequent physical examinations will be performed as per the applicable SoA (Section 1.3). At Investigator discretion, these subsequent exams can be either full or abbreviated (ie, symptom-directed to include body systems as the Investigator considers medically appropriate).

Information about each physical examination must be present in the source documentation at the study site.

Findings on physical examination that a) were present at the time of the participant providing signed informed consent **and** b) are considered clinically significant by the Investigator are to be recorded (under “Physical Examination”) as medical history in the eCRF.

Findings on physical examination that occur after the participant has provided signed informed consent, and which are considered clinically significant by the Investigator and meet the definition of an AE (or SAE) as detailed in Section 10.2, must be recorded as an AE (or SAE) in the eCRF. All SAEs must be reported as detailed in Section 10.2.4.

8.3.1.2. Body Weight and Height

Body weight (in kg) will be measured by study site staff under the following conditions: participant in light clothing and without shoes, after having emptied his/her bladder.

The participant's height (in cm) will be measured (without shoes) at Screening only, in order to calculate the body mass index.

8.3.2. Vital Signs

Vital signs collected during the study will include body temperature, systolic and diastolic blood pressure, pulse rate (after 5 minutes resting), and respiration rate. Vital signs will be measured at the time points specified in the applicable SoA (Section 1.3) with participants resting for at least 5 minutes in a supine position.

When the time of vital sign measurement coincides with a blood draw, the vital signs will be taken before the scheduled blood draw where possible, ensuring that the blood draw is within the window specified in the protocol (refer to the applicable SoA [Section 1.3]).

In the event of an abnormality that is considered clinically significant by the Investigator, and/or meets the definition of an AE (or SAE) as detailed in Section 10.2, vital sign assessments will be repeated at Investigator discretion. All repeat vital sign values should be entered on an unscheduled eCRF page.

8.3.3. Electrocardiograms

A standard 12-lead ECG will be taken at the time points specified in the applicable SoA (Section 1.3). Additional ECGs may be performed at any other time point as clinically indicated per Investigator discretion.

ECGs will be performed prior to vital signs collection, with participants in a supine position. Participants should remain in this position for at least 5 minutes before the ECG reading is taken.

The following ECG parameters should be evaluated by the Investigator:

- Heart rate
- QT interval
- PR interval
- QRS interval
- RR interval
- ST segment
- QTcF

All ECG tracings will be reviewed by the Investigator or designee.

If the QTcF exceeds 480 ms in a male participant or 500 ms in a female participant, or the QRS interval exceeds 120 ms in any participant, the ECG should be repeated in triplicate. If a repeat of an ECG is necessary for any other reason considered clinically significant by the Investigator, the repeat is not required in triplicate.

When the time of ECG monitoring coincides with a blood draw, the ECG will be taken before the scheduled blood draw while ensuring that the blood draw is within the window specified in this protocol (refer to the applicable SoA [Section 1.3]).

8.3.4. Clinical Safety Laboratory Tests

Refer to Section 10.8 for details of the specific clinical safety laboratory tests (including hematology, serum chemistry, urinalysis, and coagulation) that are to be collected during the study.

Clinical safety laboratory tests will be performed at the time points specified in the applicable SoA (Section 1.3) and will be analyzed by local laboratory. Only selected safety labs will be collected at scheduled time points; the others will be collected, per Investigator discretion, only as clinically indicated for safety monitoring purposes.

- For participants in the aumolertinib with chemotherapy arm, safety laboratory test results should be obtained and reviewed by the Investigator prior to study drug dosing.
- For participants in the aumolertinib monotherapy and osimertinib monotherapy arms, safety lab assessments should be performed pre-study drug dosing if any such assessment(s) may impact treatment decisions for the individual participant in the judgment of the Investigator.

Additional safety laboratory tests may be performed at other times if deemed necessary (per Investigator discretion), based on the participant's clinical condition.

Findings from safety laboratory assessments performed after the participant has provided signed informed consent that are considered clinically significant by the Investigator, and which meet the definition of an AE (or SAE) as detailed in Section 10.2, must be recorded as an AE (or SAE) in the eCRF. All SAEs must be reported as detailed in Section 10.2.4.

8.3.5. Pregnancy Testing

For all female participants of childbearing potential, a serum or urine pregnancy test will be performed at Screening as per the applicable SoA (Section 1.3).

Additionally, all female participants of childbearing potential who are not using contraception (and therefore must agree to be abstinent to comply with the study requirements; refer to Section 10.3.2) will have a serum or urine pregnancy test performed during each dosing visit, prior to dosing with any study intervention.

Additional serum or urine pregnancy tests may be performed to establish the absence of pregnancy at any other time during the study, if determined to be medically necessary by the Investigator or required by local regulations.

8.4. AEs, SAEs, and Other Safety Reporting

The definitions of AEs and SAEs are provided in Section 10.2.

Adverse events will be reported by the participant or, when appropriate, by a caregiver or surrogate.

All AEs (including SAEs) occurring during the study will be reported in the eCRF, regardless of whether or not attributed to study intervention and whether or not observed by the Investigator or the participant. In any circumstance, every effort should be made to document participant outcome if at all possible.

As detailed in Section 10.2.4, all SAEs occurring during the study must be reported via email to BOTH [redacted] and [redacted] using SAE Form, along with any other supporting information, and must be recorded in the AE section of the eCRF. The outcome of any ongoing SAEs should be documented, if possible.

For participant deaths, the working diagnosis or cause of each death—as stated on a death certificate, available autopsy report(s), and/or relevant medical report(s)—should be sent promptly to both the Sponsor and the Parexel Pharmacovigilance Group.

Definite progression of the disease under study, including signs and symptoms of progression as assessed by the Investigator, should **not** be reported as an AE or SAE.

- **Note:** Death unequivocally due to disease progression, as agreed by both the Investigator and the Medical Monitor, should be documented in the eCRF but should not be reported as an SAE.

The Investigator and any qualified designee(s) are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and should make every effort to document participant outcome if at all possible.

The methods of recording, evaluating, and assessing the causality of AEs and SAEs, and the procedures for completing and transmitting SAE reports, are detailed in Section 10.2.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

In this study, AEs will be reported for all participants from the time of providing signed informed consent through the completion of the participant's final follow-up visit. SAEs will be reported for all participants (enrolled and not enrolled) from the time of obtaining signed informed consent.

Medical occurrences that begin before obtaining signed informed consent will be recorded as medical history/current medical conditions, **not** as AEs.

AEs that are ongoing at the final follow-up visit will be marked as "Not Recovered/Not Resolved" on the AE eCRF page.

All SAEs will be recorded using the SAE Form, along with any other supporting information, and will be recorded in the AE section of the eCRF and reported via email to BOTH [redacted] and [redacted] within 24 hours of awareness as described in Section 10.2.4.

The Investigator will submit any updated SAE data to BOTH the Sponsor and the Parexel Pharmacovigilance Group within 24 hours of discovery or notification of the event, as detailed in Section 10.2.4.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the participant's study participation; however, in any circumstance, every effort should be made to document the outcome of the event if possible.

If the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study—and if the Investigator considers the event to be reasonably related to treatment with any study intervention, or to study participation—**the Investigator must notify the Sponsor promptly (within no more than 24 hours of awareness).**

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant, or the assigned caretaker (with the participant's written approval), is the preferred method to inquire about AE occurrences.

Any post-baseline findings in the study that are considered clinically significant by the Investigator **and** meet the definition of an AE (or SAE, as applicable) must be recorded as AEs (or SAEs). All SAEs must also be reported as detailed in Section 10.2.4.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.2.

Participants who discontinue from study treatment but do not withdraw overall consent will remain in the study for safety and survival follow-up, as detailed in the applicable SoA (Section 1.3).

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification of an SAE (within 24 hours of awareness; refer to Section 10.2.4 for full details of SAE recording and handling) by the Investigator to BOTH the Sponsor and the Parexel Pharmacovigilance Group is essential. This is required so that legal obligations and ethical responsibilities toward the safety of participants, and the safety of a study intervention that is under clinical investigation, are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority/agencies, IRBs/IECs or such other entity as required, and Investigators.

An Investigator who receives an Investigator safety report describing an SAE, or other specific safety information (eg, summary or listing of SAEs), from the Sponsor will review and then file it along with the IB/package insert and will notify the IRB/IEC if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs (refer to Section 10.2.4) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

The Investigator will be responsible for safety reporting to local IRBs/IECs, or such other entity as required, in accordance with applicable local laws and regulations.

8.4.5. Pregnancy

Details of any pregnancy in a female participant and (if applicable) any female partner of a male participant will be collected after the participant's exposure to the investigational product, and will be followed (to term) to determine the outcome.

If any such pregnancy is reported in this study, the Investigator will record pregnancy information on the Pregnancy Reporting and Outcome Form.

The completed form is then to be submitted to the Sponsor within 24 hours of learning of the pregnancy.

For pregnant female partners of male participants, the necessary signed informed consent must be obtained by the partner signing the separate Pregnant Partner ICF.

While pregnancy itself is not considered to be an AE (or SAE), any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE, as applicable.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such per Section 10.2.4.

The pregnant female participant, or pregnant female partner of a male participant (after obtaining the necessary informed consent from the latter), will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the pregnant participant/pregnant partner and (if applicable) the neonate, and this information will be forwarded to the Sponsor.

Any post-study pregnancy-related SAE that is considered by the Investigator to be reasonably related to treatment with any study intervention will be reported to the Sponsor as described in Section 10.2.4. While the Investigator is not obligated to actively seek this information from former study participants/pregnant partners of former study participants, the Investigator may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.6. Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Definite progression of the disease under study, including signs and symptoms of clinical progression as assessed by the Investigator, should not be reported as an AE or SAE—**unless** the signs and symptoms are more severe than expected for the participant's condition.

Death unequivocally due to disease progression, as agreed by both the Investigator and the Medical Monitor, should be documented in the eCRF but not reported as an SAE.

The Investigator and any qualified designee(s) are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE (refer to Section 10.2), and should make every effort to document the outcome of the event, if possible.

The methods of recording, evaluating, and assessing the causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.2.

For overdoses (Section 6.6) that are associated with an AE or SAE, the standard reporting timelines apply as detailed in Section 10.2.3.

8.5. Pharmacokinetic Assessments (Aumolertinib and Aumolertinib with Chemotherapy Arms Only)

Blood samples of approximately 4 mL each are to be collected from all participants in the aumolertinib arm and the aumolertinib with chemotherapy arm (not the osimertinib arm) for PK analyses. Refer to the SoAs in Table 1 and Table 2, respectively.

Specifically, the PK samples collected will be analyzed for measurement of plasma concentrations of aumolertinib and its metabolite HAS-719 (and other metabolites, if applicable), using a validated bioanalytical method in compliance with all applicable regulatory requirements.

The actual date and time (24-hour clock time) of each sample collection will be recorded in the source documents and in the eCRF.

Details of PK sample collection, processing, and shipment will be provided in the laboratory manual.

8.6. Patient-reported Outcomes and Quality of Life Assessments

Patient-reported outcomes and QoL will be assessed for all participants, as indicated in the applicable SoA (Section 1.3), via NCI PRO-CTCAE® questionnaire (Appendix 10). In accordance with the official PRO-CTCAE Terms of Use (NCI 2022), the instrument is intended for use to capture symptomatic adverse events by patient self-report in study participants ≥ 7 years of age; therefore, in this study, only the participants themselves are permitted to complete the questionnaire.

Any relevant AEs/SAEs will be summarized by the same approach as described in Section 8.4.

The questionnaire will be provided in either paper or electronic format and should be completed by the participant using a recall period of the previous 7 days. All data generated by study participants will be captured on a paper device or in an electronic PRO device or online portal.

Whenever possible, the NCI PRO-CTCAE questionnaire should be completed before other study procedures are performed. If the participant is unable to complete the questionnaire when scheduled, the reason for not completing the questionnaire should be documented.

8.7. Blood Volume

- For safety laboratory assessments, average total blood volume collection per participant is up to approximately 120 mL (across all study participants, an estimated collection of approximately 20 mL per sample and average of 6 samples collected per participant; depending on their duration of study participation, some participants will have fewer or more samples collected).
- For ctDNA assessments, total blood volume collection per participant is approximately 80 mL (approximately 20 mL per sample and 4 samples per participant).

- For PK assessments in participants in the aumolertinib arm and aumolertinib with chemotherapy arm—ie, not the osimertinib arm—total blood volume collection per participant is up to approximately 24 mL (approximately 4 mL per sample and 6 samples per participant).

Thus, the total blood volume collection per participant is anticipated to be up to approximately 225 mL for scheduled assessments and up to 300 mL when accounting for any potential extra (ie, repeat or unscheduled) assessments.

8.8. Biomarkers and Immunogenicity Assessments

There are no immunogenicity assessments in this study.

All study participants will be required to provide urine and blood (plasma) samples, including plasma samples for ctDNA analysis, at the time points specified in the applicable SoA (Section 1.3). Participants will also have imaging assessments performed as specified in the applicable SoA.

In addition, participants may consent to provide archival tumor tissue (FFPE or unstained slides) for CDx testing (refer to Section 8.1.5) if such tissue is available (regardless of when it was obtained); however, this is **optional** and not a study requirement.

The samples collected in the study will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity.

With participants' additional consent, the samples collected in the study may be used for further future research by the Sponsor—or by other researchers, such as those at universities or other companies—provided that participants' confidentiality is maintained. The aim of conducting such further future research is to contribute to the understanding of EGFR-mutant NSCLC or other diseases, and/or the development of related or new treatments or research methods.

Unless a longer time limitation is required by local regulations or ethical requirements, the Sponsor may store the collected plasma and urine samples until all study research objectives have been met or valid study results have been obtained. With participants' additional consent, the Sponsor may store the collected imaging and tissue samples at a central repository for up to 25 years after the end of the study (as defined in Section 4.4), in order to achieve further future research objectives.

If participants do **not** provide their additional consent for further future research use, any of their samples that remain will be destroyed after the protocol-specified study objectives have been met and all regulatory obligations have been fulfilled.

All samples collected from study participants will be transported, stored, accessed, and processed in accordance with applicable regulatory requirements and laws.

8.9. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

The study SAP will be finalized prior to database lock. The SAP will include a more technical and detailed description of the statistical analyses described in this section of the protocol, which is a summary of the planned statistical analyses of the most important endpoints.

9.1. General Considerations

Summary statistics for continuous variables will include, at the very least, n; median; mean; standard deviation; minimum; and maximum. For categorical variables, frequencies and percentages will be presented. For time-to-event variables, the Kaplan-Meier method will be used for descriptive summaries. Graphical displays will be provided as appropriate.

The primary analysis will be performed when approximately 251 PFS events have occurred in the aumolertinib with chemotherapy and osimertinib monotherapy treatment arms, as based on BICR assessment.

9.1.1. Statistical Hypotheses

The hypotheses for the primary study endpoint of BICR-assessed PFS are as follows:

- H_0: $S_{aumo\ chemo}(t) = S_{osi}(t)$
- H_A: $S_{aumo\ chemo}(t) > S_{osi}(t)$,

where $S_{aumo\ chemo}(t)$ is the function of PFS for the aumolertinib with chemotherapy arm and $S_{osi}(t)$ is the PFS for the osimertinib monotherapy arm.

9.1.2. Determination of Sample Size

Assuming a randomization ratio of 1:1 for aumolertinib with chemotherapy:osimertinib monotherapy, a true HR of 0.7 (median PFS improves from 19 months to 27.1 months), and an exponential distribution for PFS, 251 PFS events will provide 80% power at a 2-sided Type I error of 0.05. If the result of the primary endpoint analysis is statistically significant, a sequential testing method will be used to test the key secondary endpoint of OS to control the overall Type I error for the study at 2-sided 0.05. Assuming a true HR of 0.70 (ie, median OS improves from 38.6 months to 55.1 months) and an exponential distribution for OS, 200 OS events will provide 71.1% power at a 2-sided Type I error of 0.05.

Approximately 400 participants in total will be enrolled in the aumolertinib with chemotherapy and osimertinib monotherapy arms (200 per arm) to reach 251 PFS events. The sample size of 100 participants in the aumolertinib monotherapy arm will allow the precision of estimating an incidence rate for toxicity—in terms of TEAEs, ≥ Grade 3 TEAEs, SAEs, and AEs of clinical interest—to be within ± 10.3% (eg, incidence rate, 50%; Clopper-Pearson 95% CI, 39.8%, 60.2%). Therefore, approximately 500 total participants are planned to be randomized in the study in a 2:2:1 ratio to receive aumolertinib in combination with chemotherapy, osimertinib monotherapy, or aumolertinib monotherapy, respectively.

Cytel East® version 6.5 was used for the sample size calculations.

9.1.3. Interim Analysis

Two interim analyses are planned, as follows:

- The first interim analysis will be performed approximately 12 weeks after enrollment is completed.
- The second interim analysis will be performed upon occurrence of 70% of the projected PFS events.

The interim analyses will include PFS and the other endpoints listed below:

- ORR and DCR
- ctDNA clearance
- TGR
- AEs

The Lan DeMets approach, which approximates the O'Brien-Fleming spending function, will be used to maintain an overall 2-sided 0.05 Type I error for the primary PFS comparison.

The key secondary endpoint of OS (aumolertinib + chemotherapy combination therapy compared with osimertinib monotherapy) will be tested sequentially at a 2-sided 0.05 Type I error if the result of the primary endpoint analysis (PFS) is statistically significant. Formal interim OS analyses will be conducted at the time of the primary PFS analysis if the PFS analysis is positive (at one of the interim analyses, or at the final PFS analysis) and at all subsequent planned analysis points. Type I error for OS will also be controlled using Lan-DeMets method with O'Brien-Fleming boundary.

9.2. Definition of Statistical Analysis Sets

9.2.1. Full Analysis Set

The Full Analysis Set (FAS) will include all randomized participants. Participants will be analyzed in the treatment arm to which they were randomized, and strata (with stratification by EGFR mutation, ECOG PS, and race) will be assigned at the time of randomization.

9.2.2. Safety Analysis Set

The Safety Analysis Set (SAS) will include all participants who received at least one dose of study intervention. Safety data will be summarized based on the actual treatment received.

9.2.3. Pharmacokinetic Analysis Set

The PK Analysis Set will include all participants in the Safety Analysis Set who received at least one dose of aumolertinib and have at least one non-missing data collection for aumolertinib and/or its metabolite HAS-719.

Participants with protocol violations will be assessed on an individual basis for inclusion in the PK Analysis Set.

9.3. Definitions for Efficacy Endpoints

The following definitions apply to the primary, secondary, and exploratory efficacy endpoints:

- **PFS:** Defined as the time from date of participant randomization to either the first date of disease progression (as assessed per RECIST v1.1) or the date of death by any cause, whichever occurs first.
- **OS**: Defined as the time from randomization until the date of death due to any cause.
- **ORR:** Defined as the proportion of participants who achieve a CR or PR at any time before PD or initiating a subsequent anticancer therapy.
- **DCR:** Defined as the proportion of participants who have a best overall response of CR or PR or SD.
- **DoR:** Defined as the time from the date of first response (CR or PR) until the date of PD or death due to any cause, whichever occurs first.
- **DepOR:** Defined as the relative change in target lesion tumor size (calculated as the sum of the longest diameters of the target lesions, in the absence of new lesions or progression of nontarget lesions) as compared to baseline.
- **ctDNA clearance at 6 weeks:** Defined as when a detectable EGFR mutation in ctDNA at baseline becomes undetectable or drops below a predetermined threshold at 6 weeks. Rate of ctDNA clearance is defined as:

$$100 \times \frac{\text{Number of Participants who are ctDNA–negative at 6 weeks}}{\text{Number of Participants who are ctDNA–positive at baseline}}$$

- **TGR:** Defined as the constant exponential growth rate estimated using the sum of longest diameters based on radiological tumor assessment per RECIST v1.1.
- **PFS2:** Defined as the time from randomization until the date of the first progression event subsequent to that used in the primary analysis of PFS, or death due to any reason, whichever occurs first.
- **TFST:** Defined as the time from randomization to the start date of the first anticancer therapy subsequent to the discontinuation of the study intervention, or death due to any reason, whichever occurs first.
- **TSST:** Defined as the time from randomization to the start date of the second subsequent anticancer therapy after the discontinuation of the study intervention, or death due to any reason, whichever occurs first.

9.4. Statistical Analyses

9.4.1. Participant Disposition

All participants' enrollment, randomization, and treatment start/ending dates, as well as reasons for discontinuation from study treatment (randomized population) and reasons for discontinuation from study (randomized population), will be listed. Reasons for discontinuation from study treatment and from the overall study will also be summarized.

9.4.2. Demographics and Baseline Disease Characteristics

Participants' demographics and baseline disease characteristics will be listed and summarized.

Participants' medical history and prior medications/procedures will be listed.

9.4.3. Efficacy Analyses

All efficacy analyses will be performed on the FAS population, based on the treatment arm assigned in the randomization.

Response assessment (per RECIST v1.1) will be based on BICR for the primary endpoint, and on both BICR and Investigator assessment for the secondary tumor-based efficacy endpoints.

9.4.3.1. Primary Endpoint Analysis

The primary endpoint of PFS as determined by BICR (per RECIST v1.1) will be analyzed when 251 PFS events are reached in the aumolertinib with chemotherapy and osimertinib monotherapy treatment arms. The primary analysis of PFS will be based on BICR assessment and will use the stratified log-rank test to compare aumolertinib with chemotherapy combination therapy with osimertinib monotherapy (2-sided 0.05 level).

The median event time will be evaluated with a 95% CI for each treatment arm, using the Kaplan-Meier method. HRs with a 95% CI will be estimated by a stratified Cox proportional hazard model, using the Breslow method of tie handling, with treatment as the factor. The strata will be the same stratification factors (EGFR mutation, ECOG PS, and race) used in the randomization.

9.4.3.2. Key Secondary Endpoint Analysis

The final OS analysis will be performed when 200 OS events are reached in the aumolertinib with chemotherapy and osimertinib monotherapy treatment arms. The OS comparison of aumolertinib + chemotherapy combination therapy with osimertinib monotherapy will be tested sequentially at a 2-sided 0.05 Type I error if the result of the primary endpoint analysis (PFS) is statistically significant. The OS comparison will use the same methods as used for the primary PFS analyses.

9.4.3.3. Other Secondary Endpoint Analyses

The other secondary endpoints will be analyzed by the following comparisons:

- aumolertinib + chemotherapy combination therapy compared with osimertinib monotherapy
- aumolertinib monotherapy compared with osimertinib monotherapy

Secondary tumor-based efficacy endpoints will include both BICR and Investigator assessments performed per RECIST v1.1.

Statistical comparison will be at nominal significance level of 0.05 based on 2-sided tests.

9.4.3.3.1. Secondary Binary Endpoints

Secondary binary endpoints, including ORR, DCR, and the rate of ctDNA clearance at 6 weeks, will be analyzed using the CMH test stratified by the randomization stratification factors. The CMH estimate of the odds ratio with a 95% CI will be reported.

A 2-sided p-value will be provided to compare aumolertinib + chemotherapy combination therapy with osimertinib monotherapy, and aumolertinib monotherapy with osimertinib monotherapy. For each arm, the point estimate for ORR, DCR, and the rate of ctDNA clearance at 6 weeks with its exact 95% CI will be provided.

9.4.3.3.2. Secondary Time-to-Event Endpoints

Other time-to-event secondary endpoints, including PFS, DoR and OS, will be analyzed using the stratified log-rank test and the stratified Cox proportional hazard model, as described above for the primary endpoint analysis.

Specifically, these secondary endpoint analyses will be performed to compare aumolertinib + chemotherapy combination therapy with osimertinib monotherapy, and aumolertinib monotherapy with osimertinib monotherapy. The median event time will be evaluated with a 95% CI using the Kaplan-Meier method.

9.4.3.3.3. Analysis of DepOR

DepOR will be analyzed among participants with measurable lesions at baseline. Absolute and percentage change from baseline in target lesion tumor size (calculated as the sum of the longest diameters of target lesions) will be summarized using descriptive statistics at each visit for all 3 treatment arms. The best DepOR values will be calculated from assessments before disease progression or before starting subsequent anticancer treatment.

9.4.3.3.4. Analysis of TGR

TGR will be analyzed based on the sum of longest diameters over time, using the R package *tumgr* (Wilkerson 2016), which is based on the regression-growth models proposed by Stein, et al (Stein 2011).

Participants who have measurable disease at baseline and at least 1 post-baseline tumor assessment will be included in the TGR analyses. The estimated participants' TGRs will be summarized by treatment arm. Boxplots of the TGRs will be generated side-by-side to visualize TGRs for each arm. For all 3 arms, the estimated median TGR value with its 95% Wilcoxon CI will be reported.

A detailed TGR analysis plan will be included in the study SAP.

9.4.3.4. Exploratory Endpoint Analyses

9.4.3.4.1. Description of CNS Efficacy

CNS efficacy will be assessed on a subset of the FAS population, to include all participants in all 3 treatment arms who have been identified as having at least 1 measurable brain lesion at baseline based on Investigator assessment.

CNS efficacy endpoints will include PFS, OS, DoR, ORR, DCR, and DepOR, each based on Investigator assessment of CNS scans.

For time-to-event CNS endpoints, including PFS, OS, and DoR, the median event time will be evaluated with a 95% CI for each treatment arm using the Kaplan-Meier method.

For binary CNS endpoints, including ORR and DCR, the point estimate of the rate with its exact 95% CI will be calculated for each arm.

DepOR will be analyzed using the same method as for the secondary endpoint of DepOR.

9.4.3.4.2. Analysis of PFS2, TFST, and TSST

Time-to-event endpoints of PFS2, TFST, and TSST will be analyzed for all 3 treatment arms. The median event time will be evaluated with a 95% CI for each treatment arm using the Kaplan-Meier method.

9.4.4. Safety Analyses

Safety analyses will be performed on the SAS and will be presented by the actual treatment arm. Details of the safety analyses will be described in the SAP.

9.4.4.1. Exposure

Exposure parameters (including cumulative total actual dose, total/actual exposure time, actual dose intensity, relative dose intensity, and compliance) of each study intervention will be summarized using descriptive statistics.

9.4.4.2. AEs

Adverse events coded by MedDRA and graded per NCI CTCAE version 5.0 will be presented in tables and listings, using MedDRA system organ class and preferred term.

The incidence rate of TEAEs will be presented in summary tables. TEAEs are defined as AEs that start on or after the first dose of any study intervention, through 28 days after the last dose of any study intervention. Any events that start after 28 days after the last dose of any study intervention, or after a participant receives a subsequent anticancer therapy, will be included in the data listing but will not be considered as a TEAE.

Statistical analysis of AEs will utilize the Investigator-assessed relationship between study intervention and the occurrence of each AE, as detailed in Section 10.2.1.

In the event that a participant has repeat episodes of the same AE, the event with the highest severity and/or strongest causal relationship to treatment will be used for the purpose of statistical tabulations.

9.4.4.3. Physical Exam Findings

For physical exams (full and symptom-directed), findings considered clinically significant by the Investigator that were present before the participant provided signed informed consent will be reported as medical history; findings considered clinically significant by the Investigator that occurred after the provision of signed informed consent, and which meet the definition of an AE (or SAE, as applicable) as detailed in Section 10.2, will be reported as AEs/SAEs.

9.4.4.4. Vital Signs

For each treatment arm, the actual value and the change from baseline to each parameter on study evaluation will be summarized for vital signs including body temperature, systolic and diastolic blood pressures, pulse rate (after 5 minutes resting), and respiration rate.

9.4.4.5. Electrocardiograms

ECG results will be summarized descriptively. Actual values and changes from baseline will be reported for each study visit.

9.4.4.6. Clinical Laboratory Tests

For each treatment arm, the actual value and the change from baseline to each parameter on study evaluation will be summarized for selected clinical laboratory tests.

The severity of selected laboratory tests will be evaluated by NCI CTCAE version 5.0 criteria if the tests have a corresponding CTCAE classification.

9.4.5. Patient-reported Outcomes and Quality of Life Analyses

PROs and QoL will be assessed via item subset of NCI PRO-CTCAE questions. A descriptive summary over time will be provided.

9.4.6. Pharmacokinetic Analyses

Plasma concentrations of aumolertinib and its metabolite (HAS-719) will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum).

Details of population PK modeling, including data processing and statistical methodologies, will be provided in a separate pharmacometrics analysis plan. Data from this study may be combined with data from other aumolertinib studies for the population PK analysis.

Additional analyses such as exposure-response analysis to evaluate the relationship between aumolertinib exposure and efficacy/safety endpoints in this study may be performed if the data allows for this analysis to be completed.

Results of the population PK and exposure-response analyses may be summarized in a separate report, rather than in the clinical study report.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines applicable to the countries where the study is conducted
- Applicable ICH GCP Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents must be submitted to the IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- The decision of whether a formal protocol amendment is needed to accommodate administrative changes (ie, those not affecting the participant benefit/risk ratio) will be made in accordance with current ICH GCP Guidelines and all other applicable guidelines in the countries where the study is conducted. Administrative changes may be conveyed to study Investigators and sites via a protocol clarification letter compliant with ICH GCP and all other applicable guidelines.
- Protocols and any substantial amendments to the protocol will require approval from the Health Authority/ies and the IRB/IEC (for site initiation/implementation) prior to initiation of the protocol or overall implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for overall conduct of the study at the site, and adherence to requirements of 21 Code of Federal Regulations (CFR; US); ICH GCP Guidelines; the IRB/IEC; European Regulation 536/2014 for clinical studies (if applicable) and any subsequent amendments thereof; and all other applicable local regulations.
- The Investigator or designee will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by the procedures of the IRB/IEC, in accordance with the study safety reporting rules (refer to Section 10.2)

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with accurate financial information in accordance with all applicable local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities and IRB/IEC. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant in simple layperson's terms and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent (ie, ICF) that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the requirements of the study center and IRB/IEC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version(s) of the ICF(s) during their participation in the study.

A copy of the signed ICF(s) must be provided to the participant and the site must document the provision of the signed copy to each participant or representative. The signed copy of the ICF should be filed with the participant's case history.

Prospective participants who are re-screened are required to sign another ICF if the re-screening occurs more than 28 days after the initial Screening. No more than one re-screening may occur for any individual.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB/IEC.

Original signed ICFs will be maintained at the site and be made available for inspection, as appropriate.

10.1.4. Data Protection

Participants will be assigned a unique pseudonymized participant number by the Sponsor or designee. Any participant records or datasets that are transferred to the Sponsor or designee will contain the pseudonymized identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used and disclosed by the Sponsor or designee in accordance with local data protection law, the ICF, and any additional consents obtained from the participant.

The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the ICF.

The ICF must notify the participant that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor or designee, by appropriate members of the IRB/IEC, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Committee for Blinded Independent Central Review

A central, blinded Independent Review Committee will evaluate all images collected during the study for the primary endpoint of BICR-assessed PFS. BICR will also be used to assess the secondary tumor-based efficacy endpoints in the study.

A central imaging vendor will be used to collect and assess images for determination of the primary and relevant secondary study endpoints, and for management of participant treatment.

A separate charter will define the procedures used by this committee for the purposes of BICR.

10.1.6. Dissemination of Clinical Study Data

A summary of the results of the clinical study, together with a summary that is understandable to a layperson, will be provided after the global end (or early termination) of the study in all countries concerned to ensure full availability of all clinical data under this protocol, within 12 months.

10.1.7. Data Quality Assurance

Quality tolerance limits (QTLs) for this study will be predefined in the electronic trial master file (eTMF) to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.

10.1.7.1. Study Monitoring

Qualified representatives of the Sponsor or Sponsor designees (study monitors) will monitor the study according to a predetermined monitoring plan. The Investigator must permit the study monitors to periodically review all eCRFs and source documents supporting the participation of each participant in the study. The eCRFs and other documentation supporting the study must be kept up to date by the Investigator and the staff at the study site.

These study materials must be available for review by the study monitor, and/or other qualified representatives of the Sponsor, at each monitoring visit (onsite or remote) and must be provided in a way such that the participant's confidentiality is maintained in accordance with local institution, state, country, and federal requirements.

10.1.7.2. Audits and Inspections

At some point during or after the study, an audit may be performed by appropriately qualified personnel from the Sponsor's Quality Assurance group or their authorized representative.

During any such audit, the Investigator agrees to give the auditor direct access to all relevant documents supporting the eCRFs and other study-related documents, and to discuss any findings with the auditor.

Additionally, a representative from a regulatory agency may visit the Investigator at any point during or after the study to conduct an inspection of the study and the site.

In the event of any such inspection, the Investigator agrees to give the inspector direct access to all relevant documents and to discuss any findings with the inspector.

10.1.7.3. Quality Control and Quality Assurance

eCRFs must be completed for each participant enrolled. Each completed eCRF, as well as records for all participants who are screen failures or discontinue the study, will require a signature by the Principal Investigator at the study site.

If a participant withdraws from the study, the reason must be noted on the eCRF, and if a participant is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRFs and in all required reports.

Accurate and reliable data collection will be assured by verification and cross-check activities (eg, the study monitor checking representative eCRFs against the Investigator's records [source document verification]) and maintenance of a drug-dispensing log by the Investigator. A comprehensive validation check program will be used to verify data and discrepancy reports will be generated accordingly for resolution by the Investigator.

Review of eCRFs, and validation/edit checks to identify and resolve discrepancies, will be performed throughout the study. Investigator signatures will be collected upon completion of eCRF review. eCRFs are not considered a study data source but are used to record participant data relating to the study unless such data are transmitted to the Sponsor or designee electronically (eg, PK data, biomarker data).

The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF. Guidance on completion of eCRFs will be provided in a separate technical document.

The Investigator must permit study audits and inspections according to Sponsor, IRB/IEC, and regulatory requirements and must provide direct access to source data documents.

Monitoring details describing strategies, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the monitoring plan.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period.

No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

All data generated by the study site personnel will be captured electronically in Veeva Vault Electronic Data Capture, a 21 CFR Part 11-compliant system.

All data generated by the participants in the study will be captured via a paper or electronic PRO device that is 21 CFR Part 11-compliant. These devices will be considered a study data source.

10.1.8. Source Documents

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

Data reported in the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing targeted data verification and ongoing review of participant source records to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8.1. Records Retention

After closure of the study, the Investigator will maintain copies of all study records (ie, Investigator files and participant files) in a secure location.

The Investigator's study file will contain the protocol, protocol amendments, eCRF and query forms, IRB/IEC approval with correspondence, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Participant clinical source documents may include (but are not limited to) participant hospital records, physician's and nurse's notes, original laboratory reports, ECGs, X-rays, signed ICFs, consultant letters, and participant screening and enrollment logs.

These documents must be kept on file by the Investigator for a period of 2 years following the date the marketing application is approved for the drug indication for which it is being investigated, or as otherwise specified by local regulations.

If no application is to be filed or if the application is not approved for such indication, all records pertaining to the conduct of the clinical study must be adequately maintained until 2 years after the investigation is discontinued and the regulatory authorities are notified, or as otherwise specified by local regulations. After that period of time, the documents may be destroyed, subject to local regulations upon approval of the Sponsor.

The Investigator must not destroy any records associated with the study without receiving approval from the Sponsor.

The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records and should notify the Sponsor of any reassignment of study records to another party or move to another location.

10.1.9. Study and Site Start and Closure

10.1.9.1. First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

10.1.9.2. Study Termination

The entire study may be terminated in the event of any of the following:

- Occurrence of AEs unknown to date with respect of their nature, severity, and duration, or the unexpected incidence of known AEs
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of participants
- Cancellation of the drug development program
- Sponsor decision for any other reason, as detailed in Section 4.4

The Sponsor reserves the right to terminate the study at any time. If the study is terminated by the Sponsor, participants will not be provided further study intervention or concomitant medication.

10.1.9.3. Site Termination

The Sponsor or designee reserves the right to close any study site(s) or terminate the study at site(s) at any time for any reason at the sole discretion of the Sponsor.

The Principal Investigator may initiate study-site closure at any time and shall notify the Sponsor in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to the following:

For study termination at a site:

- Discontinuation of further study intervention development

For site termination:

- Failure of the Investigator to comply with the protocol; the requirements of the IRB/IEC or local Health Authorities; the Sponsor's procedures; or GCP Guidelines
- Inadequate or no recruitment of participants by the Investigator
- Total number of participants included earlier than expected

In the event of premature termination or suspension, the Sponsor shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements.

The Investigator shall promptly inform each participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a Coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.11. Protocol Approval and Amendments

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/IEC /Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first participant is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive approval from the IRB/IEC /Competent Authorities prior to implementation (if appropriate).

In the US: Following approval, the protocol amendment(s) will be submitted to the IND under which the study is being conducted.

The decision of whether a formal protocol amendment is needed to accommodate administrative changes (i.e, those not affecting the participant benefit/risk ratio) will be made in accordance with current ICH GCP Guidelines and all other applicable guidelines in the countries where the study is conducted. Administrative changes may be conveyed to study Investigators and sites via a protocol clarification letter compliant with ICH GCP and all other applicable guidelines.

All protocol amendments will be distributed to all protocol recipients, with appropriate instructions.

10.1.12. Liability and Insurance

The Sponsor will take out third-party liability insurance cover in accordance with all legal requirements. The civil liability of the Investigator, the persons instructed by the Investigator and the hospital, practice, or institute in which they are employed, and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for participants taking part in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

10.1.13. Access to Source Data

During the study, a monitor will make remote or onsite visits to review protocol compliance, compare eCRF entries and individual participant's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that participant confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs/IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or onsite audit inspections.

Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor, and any contract research organization or other individual or entity working on the Sponsor's behalf, if involved in monitoring/data management, of the necessary support at all times.

10.2. Appendix 2: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.2.1. Definition of an AE

AE Definition
An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • **Note**: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.
Events <u>Meeting</u> the AE Definition:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e, **not** related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency or intensity of the condition • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, per se, will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
Events <u>NOT</u> Meeting the AE Definition:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.2.2. Definition of an SAE

An SAE is an AE that meets one of the following criteria:

1. Results in death.

2. Is life-threatening.

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does **not** refer to an event which hypothetically might have caused death if it were more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization.

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious.

When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is **not** considered an AE.

4. Results in persistent or significant disability/incapacity.

The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

5. Is a congenital anomaly/birth defect.

6. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of drug dependency or drug abuse.

10.2.3. Recording and Follow-up of AEs and SAEs

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information using the AE section of the CRF and, for SAEs, the SAE Form (refer to Section 10.2.4).
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to EQRx International, Inc. and Parexel Pharmacovigilance Group in lieu of completion of the SAE Form.
- There may be instances when copies of medical records for certain cases are requested by both EQRx International, Inc. and Parexel Pharmacovigilance Group. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to EQRx International, Inc. and Parexel Pharmacovigilance Group.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The intensity of AEs should be documented using NCI CTCAE version 5.0.

For events **not listed** in the NCI CTCAE version 5.0, the intensity of AEs should be classified according to the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL (Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.)
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

The Investigator will assess the relationship between study intervention and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to study intervention will be recorded in the source documents and the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to study intervention should be considered and investigated, if appropriate.

The following definitions are general guidelines to help assign grade of attribution:

- **Not related**: The event is clearly related to other factors such as the participant's environment or clinical state, therapeutic interventions or concomitant drugs administered to the participant. This is especially so when an event occurs prior to the commencement of treatment with the study intervention.
- **Unlikely related**: The temporal association, participant history, and/or circumstances are such that study intervention is not likely to have had an association with the observed event. Other conditions, including concurrent illness, progression, or expression of the disease state, or reaction to a concomitant drug administered appear to explain the event.
- **Possibly related**: The event follows a reasonable temporal sequence from the time of study intervention administration or follows a known response to the study intervention but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.
- **Probably related**: The event follows a reasonable temporal sequence from the time of study intervention administration and follows a known response to the study intervention and cannot be reasonably explained by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs administered to the participant.
- **Definitely related**: The event follows a reasonable temporal sequence from the time of study intervention administration or control abates upon discontinuation or cannot be explained by known characteristics of the participant's clinical state.

Follow-up of AEs and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide **BOTH** EQRx International, Inc. and Parexel Pharmacovigilance Group with a copy of any available postmortem findings, including histopathology.

New or updated information will be recorded in the originally completed form.

The Investigator will submit any updated SAE data via email to **BOTH** [redacted] and [redacted] within 24 hours of receipt of the information.

10.2.4. Reporting of SAEs

SAE Reporting via Email

The Investigator must report any SAE via email to BOTH [redacted] and [redacted] within 24 hours of becoming aware of the event.

The Investigator and the Sponsor (or Sponsor's designated agent) will review each SAE report, and the Sponsor/Sponsor's designated agent will evaluate the seriousness and the causal relationship of the event to study intervention. In addition, the Sponsor (or Sponsor's designated agent) will evaluate the expectedness according to the Reference Safety Information (Investigator's Brochure or Summary of Product Characteristics).

Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

After the study is completed at a given site, the electronic data collection tool will be deactivated to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant, or receives updated data on a previously reported SAE after the EDC system has been deactivated, then the site can report this information on the paper SAE Form (refer to Section 10.2.4) or by telephone.

Contacts for SAE reporting (as detailed in Section 10.2.4.1) can also be found in the Investigator site file.

SAE Reporting via the SAE Form

Email transmission of the SAE Form is the preferred method to transmit this information.

In rare circumstances, and in the absence of email equipment, notification by telephone is acceptable. Initial notification via telephone does **not** replace the need for the Investigator to complete and sign the SAE Form within the designated reporting timeframes.

Contacts for SAE reporting (as detailed in Section 10.2.4.1) can also be found in the Investigator site file.

Serious Unexpected Serious Adverse Reactions (SUSARs)

Any AE that is serious, associated with the use of the study intervention, and unexpected—and which has a reasonable suspected causal relationship to the study intervention—is considered a SUSAR and has additional reporting requirements, as described below.

- An unexpected AE is an event or reaction that is not listed in the IB, or not listed at the specificity or severity that has been observed; for which the nature and severity is not consistent with the information about the medicinal product in question as set out in the reference safety information; or, if an IB is not required or available, is not consistent with the risk information described in the General Investigational Plan, or elsewhere in the relevant current Investigational New Drug application.
- A reasonable suspected causal relationship means that there is a reasonable possibility that the study intervention caused the AE—i.e, evidence to suggest a causal relationship.
- If the SUSAR is fatal or life-threatening, associated with study intervention, and unexpected, regulatory authorities and IRBs/IECs will be notified as soon as possible, and in any event within 7 calendar days after the Sponsor first learns of the event, or such earlier time period as required under national law.
  - Additional follow-up information for fatal or life-threatening SUSARs (e.g, cause of death, autopsy report, hospital report) should be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening—but is otherwise serious, associated with study intervention, and unexpected—regulatory authorities and IRBs/IECs will be notified as soon as possible, and in any event within 15 calendar days after the Sponsor first learns of the event, or such earlier time period as required under national law.
  - Additional follow-up information for non-fatal/non-life-threatening SUSARs (e.g, hospital report) should be reported within 15 days total.
- The Sponsor will notify the Investigators in a timely fashion of relevant information about SUSARs that could adversely affect the safety of study participants. Follow-up information may be submitted if necessary.
- The Sponsor will also provide annual safety updates to the regulatory authorities and IRBs/IECs responsible for the study. These updates will include information on SUSARs and other relevant safety findings.

10.2.4.1. SAE Contact Details

SERIOUS ADVERSE EVENT REPORTING INSTRUCTIONS
Parexel International Corporation
Parexel Safety Services
Telephone Number: +1-781-434-5010
Parexel International Email: [redacted]
EQRx Safety Email: [redacted].

Email the SAE Form and any supporting documentation to ***BOTH*** [redacted] ***AND*** [redacted] *within 24 hours of becoming aware of the event.*

Following receipt of the SAE Form, Parexel will provide a confirmation of receipt, which should be filed with the safety report. If you do not receive a confirmation of receipt within 3 working days, please re-submit the SAE report.

In the event that email is down, a Parexel Safety Contact may be reached through Parexel's voice mailbox at +1 781-434-5010 to report the SAE. Please leave the following information in your voice mail message:

- *Your name*
- *The telephone number where you can be reached*
- *The study protocol number and title*
- *The study intervention name*
- *The Principal Investigator's name*
- *The name of the Sponsoring pharmaceutical company*

10.3. Appendix 3: Contraceptive and Barrier Guidance

10.3.1. Definitions

Female Participants of Childbearing Potential

- Female participants in the following categories are considered to be **of childbearing potential** (fertile):
  - Following menarche.
  - From the time of menarche until becoming postmenopausal, unless permanently sterile (see below).

Postmenopausal and Permanent Sterilization

- A **postmenopausal** state is defined as no menses for ≥ 1 year without an alternative medical cause.
  - At Investigator discretion, a high FSH level in the postmenopausal range may be used to confirm a medically postmenopausal state in female participants who are not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 1 year of amenorrhea, confirmation with more than 1 FSH measurement is required.
  - Female participants who are on HRT and whose postmenopausal status is in doubt will be required to use one of the non-estrogen hormonal, highly effective contraception methods (refer to Section 10.3.2) if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of their postmenopausal status before study enrollment.
- **Permanent sterilization** methods (for the purpose of confirming non-childbearing potential status in this study, at Investigator discretion) include the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
  - Documented bilateral tubal ligation/occlusion

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

Notes:

- Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- If fertility status is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of any study intervention, additional evaluation should be considered.

10.3.2. Contraception Guidance

Contraceptives[a] Allowed During the Study Include the Following:
Highly Effective Methods[b] that Have Low User-Dependency ***Failure rate of < 1% per year when used consistently and correctly.***
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device
Intrauterine hormone-releasing system[c]
Bilateral tubal occlusion
Azoospermic male partner (vasectomized or due to a medical cause) • Azoospermia is a highly effective contraceptive method provided that the partner is the sole heterosexual partner of the female participant of childbearing potential (as defined in Section 10.3.1) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. • Spermatogenesis cycle is approximately 90 days. – **Note:** Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] that are User-Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulation: • oral • injectable
Sexual abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

[a] Contraceptive use by male and female participants in all treatment arms should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. Refer to the Clinical Trial Facilitation Group (CTFG) guidelines for additional information.
- All participants must follow the contraception duration requirements for the drugs they receive, in accordance with the current local label for each drug.

[b] Failure rate of < 1 % per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with CTFG guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Notes:

- Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study.
- Male condom and female condom should not be used together (due to risk of failure from friction).

10.4. Appendix 4: Hy's Law Definition, Reporting, and Observation Requirements

Hy's Law cases may be indicative of drug-induced hepatocellular injury.

The following events may indicate hepatocellular injury (Hy's Law):

- ALT or AST ≥ 3 × ULN

  and

- TBIL to ≥ 2 × ULN without initial findings of cholestasis (elevated serum ALP > 2 × ULN)

  and

- No other reason can be found to explain the combination of increased ALT or AST and TBIL.

Unless otherwise specified in the protocol, **in the event that a participant meets potential Hy's Law criteria, treatment with study intervention must be permanently discontinued**. The Investigator must notify the Sponsor as soon as possible, but no more than 24 hours later, and report the event as an SAE. SAE reporting details are provided in Section 10.2.4.

For special situations, if the first occurrence of a potential Hy's Law event is determined to be due to alternative etiology other than study intervention, the study intervention can be re-started per predefined criteria in the protocol.

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible hepatollceular injury, and not to wait until the next scheduled visit or monitoring interval.

If additional testing beyond that specified in the protocol is carried out, it is important that the testing information is added to the eCRF and safety database.

Close observation includes the following:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study intervention has been discontinued and the participant is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (eg, INR, direct bilirubin).

- Considering gastroenterology or hepatology consultations.

All participants showing possible hepatocellular injury should be followed until all abnormalities return to normal or to the baseline state. Hepatocellular injury may develop or progress even after study intervention has been stopped. Results should be recorded on the eCRF and in the safety database. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be hepatocellular injury, indicating that liver injury was related to underlying liver disease.

Refer to the US Food and Drug Administration's Guidance for Industry for additional information.

10.5. Appendix 5: Prohibited Concomitant Medications

Table 8: Examples of Prohibited Concomitant Agents Because of the Potential for Pharmacokinetic Drug-Drug Interaction with Aumolertinib[a]

Medication Class	Prohibited Agents[b]
Strong CYP3A Inhibitors	cobicistat, ritonavir, ketoconazole, voriconazole, clarithromycin, itraconazole, grapefruit[c], grapefruit juice[c]
Strong CYP3A Inducers	phenytoin, carbamazepine, rifabutin, rifapentine, rifampin, St. John's wort

[a] This table presents examples of the most common concomitant medications in relation to aumolertinib and is not an exhaustive list. Refer to the current prescribing information for osimertinib, pemetrexed, cisplatin, carboplatin, paclitaxel, albumin-bound paclitaxel, and gemcitabine for guidance on medications prohibited for concomitant use with each of these study interventions.
[b] Beginning 14 days (or 5 half-lives, whichever is longer) prior to Day 1 and through the participant's final study visit.
[c] Beginning 72 hours prior to Day 1 and through the participant's final study visit.
CYP3A = cytochrome P450 3A.

10.6. Appendix 6: Tumor Identification, Response, and Progression per RECIST v1.1

For study tumor assessments performed per RECIST v1.1, all sites of disease should be assessed radiologically by CT with contrast scan (this is the preferred imaging modality; however, PET/CT scan may instead be used at Investigator discretion) at the time points shown in the applicable SoA (Section 1.3). The same imaging modality (CT with contrast or PET/CT) should be used across all scan collections for the individual participant.

Imaging assessments will be performed (per RECIST v.1.1) by BICR for the primary study endpoint and by both BICR and Investigator for the secondary tumor-based efficacy endpoints. Objective response data collected for the clinical study report will be based on BICR and Investigator assessments as noted above.

For all participants, CT scan of the chest and abdomen/pelvis with contrast (or PET/CT scan, as applicable per Investigator discretion) is to be collected at baseline. Scans that were obtained prior to the provision of signed informed consent will not need to be repeated if they were performed within 28 days prior to the initiation of study drug dosing.

All participants with a CR must also have a CT with contrast (or PET/CT, as applicable) scan performed as part of confirmation of the CR. Additional scans may be obtained at the discretion of the Investigator, if clinically indicated. If a participant shows a radiological response (CR or PR), a confirmatory radiological assessment will be performed at least 4 weeks after the response was first noted. Participants who have a confirmed CR will have a CT with contrast (or PET/CT, as applicable) scan to confirm absence of bony metastases.

For participants who remain on therapy for 12 months following study enrollment, the timing of scans should occur as specified in the applicable SoA in Section 1.3.

Refer to Section 8.1.2.7 for additional details.

10.6.1. Definitions of Tumor Response and Disease Progression per RECIST v1.1

The determination of tumor response and progression in this study will be based on RECIST v1.1 (Eisenhauer 2009). In addition, assessment of brain metastases (as applicable) should follow RANO criteria (refer to Section 10.7).

The definitions for tumor response per RECIST v1.1 are provided immediately below.

10.6.1.1. Evaluation of Target Lesion Response

- **CR:** Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
- **PR:** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
- **PD:** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

- **SD:** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

A response category of **"NE"** is to be used when there is inadequate information to otherwise categorize the response status.

10.6.1.2. Evaluation of Nontarget Lesions

- **CR:** Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be < 10 mm short axis.
- **Non-CR/Non-PD:** Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.
- **PD:** Unequivocal progression of existing nontarget lesions or the appearance of at least 1 new lesion.

10.6.1.3. Evaluation of Overall Response

The evaluation of overall response at each time point, based on target and nontarget lesion responses at each time point as well as the appearance of new lesions, is described in Table 9.

The best overall response is the best response recorded from the start of the treatment until disease progression. Confirmation of CR and PR is required, as previously described.

Table 9: Evaluation of Overall Response per RECIST v1.1 at Each Time Point

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

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
Source: Eisenhauer 2009

10.7. Appendix 7: Definitions of Response and Progression for Brain Metastases per RANO Criteria

RANO criteria (Chukwueke 2019) definitions of response and progression, which apply to assessment of brain metastases in this study, are provided in Table 10.

Table 10: Evaluation of Response and Progression for Brain Metastases per RANO Criteria

Criterion	CR	PR	SD	PD
Target lesions	None	≥ 30% decrease in sum LD relative to baseline	< 30% decrease in sum LD relative to baseline, but < 20% increase in sum LD relative to nadir	≥ 20% increase in sum LD relative to nadir[b]
Nontarget lesions	None	Stable or improved	Stable or improved	Unequivocal PD[b]
New lesion(s)[a]	None	None	None	Present[b]
Corticosteroids	None	Stable or decreased	Stable or decreased	NA[c]
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse[b]
Requirement for response	All	All	All	Any[c]

[a] Progression occurs when this criterion is met.
[b] "New lesion" is defined as a new lesion not present on prior scans and visible in at least 2 projections.
- If a new lesion is equivocal (eg, because of its small size), continued therapy may be considered and follow-up evaluation will clarify whether it represents truly new disease.
- If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan showing the new lesion.
- For immunotherapy-based approaches, new lesions alone do not define progression.

[c] Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.
CR = complete response; LD = longest dimension; NA = not applicable; PD = progressive disease; PR = partial response; RANO = Response Assessment in Neuro-Oncology; SD = stable disease.
Source: Chukwueke 2019

10.8. Appendix 8: Clinical Safety Laboratory Tests

Clinical safety lab parameters to be tested in this study are detailed below.

Clinical safety labs for screening and enrollment purposes will be processed using a licensed laboratory/laboratory with applicable local accreditation.

10.8.1. Hematology

Hematology parameters to be tested in the study are as follows:

Hematology Parameters
Required for All Participants at Time Points Shown in the Applicable SoA **(Section 1.3):**
Absolute neutrophil count (ANC)[a]
Hemoglobin (Hgb)
White blood cells (WBC)
Platelets (PLAT)
Required Only if Clinically Indicated per Investigator Discretion:
Hematocrit (HCT)
Leukocytes (LEUK) with differential (including Eosinophils [ESN], Neutrophils [NEUT], Basophils [BASO], Lymphocytes [LYM], and Monocytes [MONO])

[a] For participants in the aumolertinib monotherapy and osimertinib monotherapy arms, ANC is required only at Screening, and then only as clinically indicated.

10.8.2. Serum Chemistry

Serum chemistry parameters to be tested in the study are as follows:

Serum Chemistry Parameters	
Required for All Participants at Time Points Shown in the Applicable SoA **(Section 1.3):**	
Alanine aminotransferase (ALT)	
Alkaline phosphatase (ALP)	
Aspartate aminotransferase (AST)	
Total bilirubin (TBIL) and indirect bilirubin (IBILI)	
Calculated creatinine clearance (CLCr)[a]	
Creatine phosphokinase (CPK)	
Creatinine (CREAT)[b]	
Glucose (GLU)[c]	
Required Only if Clinically Indicated per Investigator Discretion:	
Albumin (ALB)	Phosphate (PHOS)
Bicarbonate (BICARB)	Potassium (K)
Calcium (CA)	Sodium (NA)
Chloride (CL)	Triglycerides (TRI)

Gamma-GT (GGT)	Urea (U) or blood urea nitrogen (BUN), at site discretion
Globulin (GLOBUL)	
Magnesium (Mg)	

[a] CLCr is to be estimated by Cockroft-Gault equation.
[b] For participants in the aumolertinib monotherapy and osimertinib monotherapy arms, CREAT is required only at Screening, and then only as clinically indicated.
[c] For all participants in all 3 treatment arms, GLU is to be collected in the fasted state at Screening and non-fasted at all other time points.

10.8.3. Urinalysis

Urinalysis testing in the study will be performed by dipstick.

If an abnormality is noted for protein, blood, nitrite, or leukocyte esterase (and at the discretion of the Investigator), a microscopic examination of RBCs, WBCs, bacteria, and casts may be performed.

10.8.4. Coagulation

Prothrombin time (PT) collection/INR calculation are to be performed at Screening for all participants. Subsequently, PT/INR are to be assessed only as clinically indicated per Investigator discretion.

Any participant determined to be anti-coagulated should be monitored by local testing.

10.9. Appendix 9: Pre-Screening EGFR Mutation Testing for Prospective Study Participants (as applicable)

To be eligible for this study, all participants must have one of the required EGFR mutations present as confirmed by laboratory testing. If available, existing EGFR mutation test results may be used to confirm participant eligibility, provided that they were obtained within ≤ 3 months prior to study entry.

If recommended by the Investigator, prospective study participants for whom EGFR mutation testing is not covered or reimbursed by standard of care may undergo such testing for confirmatory purposes pre-screening.

Any such prospective participant will be required to sign the separate Pre-Screening ICF to allow blood or tissue sample collection for local EGFR mutation testing prior to the 28-day study Screening window.

At the time the prospective participant signs the Pre-Screening ICF, the Investigator should ensure that there is a reasonable possibility the individual would be a candidate for this study, in consideration of the study inclusion/exclusion criteria and based on all available information.

Once the prospective participant has signed the Pre-Screening ICF, the main study ICF is not to be signed, nor any study tests or procedures initiated, until the qualifying laboratory test result for EGFR mutation status has been obtained.

10.10. Appendix 10: Patient-Reported Outcomes Questionnaire

NCI-PRO-CTCAE® CUSTOM SURVEY

Item subset derived from PRO-CTCAE® Item Library Version 1.0
English
Form Created on 26-January-2023
https://healthcaredelivery.cancer.gov/pro-ctcae/builder.html

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days…

1a. In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
2a. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
2b. In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much
3a. In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
4a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
4b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
O Not at all	OA little bit	O Somewhat	O Quite a bit	O Very much

5a. In the last 7 days, how OFTEN did you have NAUSEA?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
5b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
6a. In the last 7 days, how OFTEN did you have VOMITING?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
6b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
7a. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
8a. In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
8b. In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
8c. In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much
9a. In the last 7 days, how OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
9b. In the last 7 days, how much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

10a. In the last 7 days, did you have any RASH?				
O Yes		O No		
11a. In the last 7 days, what was the SEVERITY of your DRY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
12a. In the last 7 days, what was the SEVERITY of your ACNE OR PIMPLES ON THE FACE OR CHEST at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
13a. In the last 7 days, did you have any HAIR LOSS?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much
14a. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
15a. In the last 7 days, did you LOSE ANY FINGERNAILS OR TOENAILS?				
O Yes		O No		
16a. In the last 7 days, did you have any RIDGES OR BUMPS ON YOUR FINGERNAILS OR TOENAILS?				
O Yes		O No		
17a. In the last 7 days, did you have any CHANGE IN THE COLOR OF YOUR FINGERNAILS OR TOENAILS?				
O Yes		O No		
18a. In the last 7 days, did you have any INCREASED SKIN SENSITIVITY TO SUNLIGHT?				
O Yes		O No		

19a. In the last 7 days, what was the SEVERITY of your PROBLEMS WITH CONCENTRATION at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
19b. In the last 7 days, how much did PROBLEMS WITH CONCENTRATION INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much
20a. In the last 7 days, what was the SEVERITY of your PROBLEMS WITH MEMORY at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
20b. In the last 7 days, how much did PROBLEMS WITH MEMORY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much
21a. In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
21b. In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
21c. In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much
22a. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
O Never	O Rarely	O Occasionally	O Frequently	O Almost constantly
22b. In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
22c. In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

23a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
O None	O Mild	O Moderate	O Severe	O Very severe
23b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
O Not at all	O A little bit	O Somewhat	O Quite a bit	O Very much

OTHER SYMPTOMS	
Do you have any other symptoms that you wish to report?	
O Yes	O No

Please list any other symptoms:					
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	O None	O Mild	O Moderate	O Severe	O Very Severe

5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?
	O None O Mild O Moderate O Severe O Very Severe

Source: PRO-CTCAE® items and information developed by the Division of Cancer Control and Population Sciences in the National Cancer Institute at the National Institutes of Health, Bethesda, Maryland, USA.

10.11. Appendix 11: Abbreviations and Definitions of Terms

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BASO	Basophils
BBB	Bundle branch block
BICARB	Bicarbonate
BICR	Blinded independent central review
CA	Calcium
CDx	Companion diagnostic(s)
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Chloride
CLcr	Creatinine clearance
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CR	Complete response
CREAT	Creatinine
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group
CTIS	Clinical Trials Information System
CYP	Cytochrome P450

Abbreviation	Definition
DCR	Disease control rate
DepOR	Depth of response
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ESN	Eosinophils
eTMF	Electronic trial master file
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLOBUL	Globulin
GLU	Glucose
HCT	Hematocrit
HDL-C	High-density lipoprotein cholesterol
Hgb	Hemoglobin
HR	Hazard ratio
HRT	Hormonal replacement therapy
IA	Interim analysis
IB	Investigator's Brochure
IBILI	Indirect bilirubin
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International Normalized Ratio

Abbreviation	Definition
IRB	Institutional Review Board
IRT	Interactive response technology
IV	Intravenous(ly)
IVRS	Interactive voice response system
IWRS	Interactive Web response system
K	Potassium
LDL-C	Low-density lipoprotein cholesterol
LYM	Lymphocytes
MATE	Multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MONO	Monocytes
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NA	Sodium
NASH	Non-alcoholic steatohepatitis
NCI	National Cancer Institute
NCI PRO-CTCAE	National Cancer Institute Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
NE	Not evaluable
NEUT	Neutrophils
NMPA	National Medical Products Administration
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small cell lung cancer
OAT	Organic anion transporting
OATP	Organic anion transporting polypeptide
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PFS	Progression-free survival

Abbreviation	Definition
PFS2	Time to second objective disease progression
P-gp	P-glycoprotein
PHOS	Phosphate
PK	Pharmacokinetic(s)
PLAT	Platelets
PR	Partial response
PRO	Patient-reported outcome
PROT	Protein
PS	Performance status
QD	Once daily
qwk	Once weekly
qXwk	Once every X weeks
QoL	Quality of life
QTc	Corrected QT interval
QTcF	QT interval with Fridericia's correction
QTL	Quality tolerance limit
RANO	Response Assessment in Neuro-Oncology
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Safety Analysis Set
SD	Stable disease
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reaction
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TFST	Time to first subsequent anticancer therapy
TGR	Tumor growth rate
TKI	Tyrosine kinase inhibitor
t_{max}	Time to maximum plasma concentration

Abbreviation	Definition
TRI	Triglycerides
TROP1	Troponin 1
TSST	Time to second subsequent anticancer therapy
U	Urea
ULN	Upper limit of normal
URATE	Urate
UROBIL	Urobilinogen
US	United States
WBC	White blood cell
WT	Wild-type

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